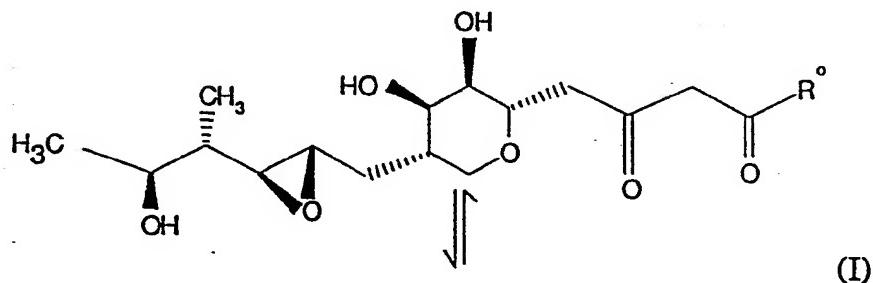




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(54) Title: ANTIBACTERIAL, ANTIMYCOPLOSMAL COMPOUNDS RELATED TO MUPIROCIN



(57) Abstract

This invention relates to a novel class of mupirocin derived compounds of Formula (I) having a modification of the C-1 to C-3 fragment. The β -diketone compounds of Formula (I) are useful as antibacterial and antimycoplasmal agents. The compounds of this invention are represented by formula (I) wherein R^0 is a hydrocarbyl or heterocyclic group.

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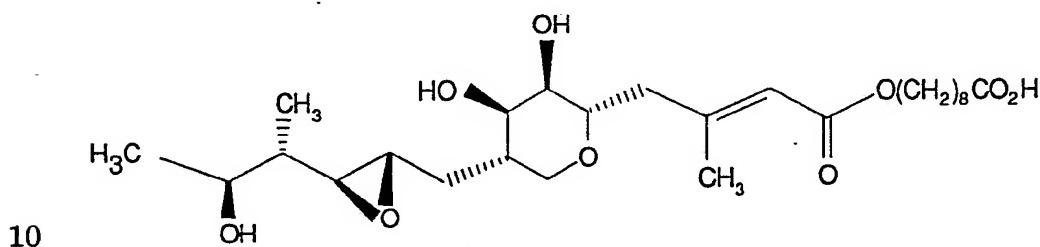
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ANTIBACTERIAL, ANTIMYCOPLASMAL COMPOUNDS RELATED TO MUPIROCIN

This invention relates to a novel class of compounds having antibacterial and antimycoplasmal activity, to processes for their preparation and to
 5 their use in human and veterinary medicine, and also to intermediates for use in the preparation of such compounds.

Mupirocin, the compound of formula (A):



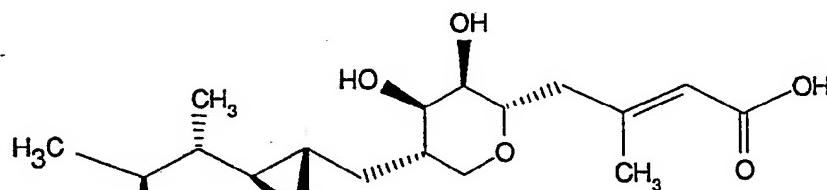
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(A)

exhibits good activity against Gram positive bacteria, H.influenzae,
Legionella and mycoplasma. It is marketed as a topical formulation by
 15 Beecham Group p.l.c. under the trade mark BACTROBAN. Mupirocin
 formerly known as pseudomonic acid is rapidly hydrolysed in vivo to
 monic acid A, the compound of formula (B):

20

(B)

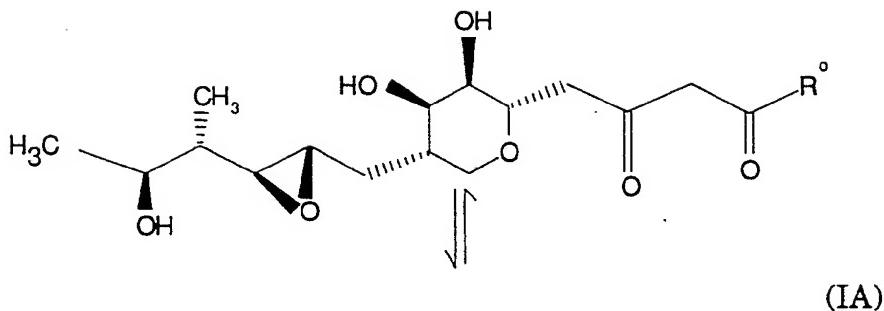


which is inactive.

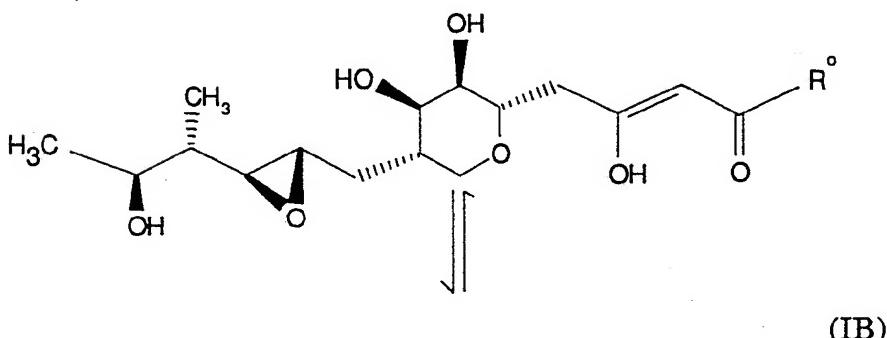
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- Various proposals have been made to improve the metabolic stability of mupirocin with respect to enzymatic hydrolysis by varying the nature of the C-1 to C-3 fragment, for instance, by modification of the C-1 ester functional group. Examples of this strategy include C-1 heterocyclic derivatives (EP-A-0 087 953 and EP-A-0 123 578, Beecham Group p.l.c.), C-1 amides (US 4 312 764, Beecham Group Ltd), and C-1 ketones, including inter alia aryl and heterocyclic ketones (US 4 312 874, Beecham Group Ltd, Klein *et al*, poster presented at the Third Annual Chemical Congress of North America, Toronto, June 1988, and *J. Med. Chem.* 1989, 32, 151). In addition, various modifications elsewhere in the C-1 to C-3 fragment, other than at C-1, have also been made, including β -ketoesters (Klein *et al*, *ibid.*), C-2 alkyl and C-2 halo derivatives (Crimmin M. J. *et al*; *J. Chem. Soc., Perkin Trans. 1*, 1985, 549), and reduction of the C-2 C-3 double bond (Chain E.B. *et al*, *J. Chem. Soc., Perkin Trans. 1*, 1977, 294). No improvement in the overall biological profile, compared with mupirocin, was, however, observed. Indeed, the β -ketoester is reported to have shown little if any antibacterial activity.
- It has now been surprisingly found that alternative modification of the C-1 to C-3 fragment leads to compounds with an enhanced biological profile.

Accordingly, the present invention provides a compound of formula (IA), (IB) or (IC):



5



10

(IC)

- wherein R^o denotes a substituted or unsubstituted hydrocarbyl or heterocyclyl group. More specifically R^o denotes the term $(A)_n - (B)_m$; wherein n and m are integers having a value of 0 or 1; A is a (C_{1-6}) alkyl, (C_{2-6}) alkenyl, or (C_{2-6}) alkynyl group; B is a (C_{3-7}) cycloalkyl, (C_{4-7}) cycloalkenyl, aryl, heterocyclyl or heteroaryl group. Both A and B may be optionally substituted as herein below defined. In the R^o moiety when n is 0 then A represents a bond, and when m is 0 then B represents hydrogen; m and n may not both represent 0 at the same time.
- 15 Suitably when n is 0 and m is 1, B is a substituted or unsubstituted (C_{4-7}) cycloalkenyl, aryl, heterocyclyl or heteroaryl group. B is preferably an aryl or heteroaryl moiety. More specifically, B is a cyclohexenyl, phenyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazolyl, oxazolyl, or thiazolyl group.
- 20

Suitably, when n is 1, m is 0, and B is hydrogen, then A is a (C₁₋₆)alkyl moiety. A is preferably a substituted or unsubstituted butyl group.

- 5 Suitably, when n is 1, and m is 1, then A is a (C₂₋₆)alkenyl, (C₂₋₆)alkynyl group. Preferably, when n is 1, and m is 1, then B is a substituted or unsubstituted aryl or heteroaryl group, such as a furanyl or phenyl. More preferably A is an ethenyl or acetylenyl (ethynyl) group.
- 10 Suitably B is a substituted or un-substituted aryl or heteroaryl group. As used herein the term "(un)substituted" refers to both the substituted and unsubstituted derivative. Preferably B is a (un)substituted phenyl, (un)substituted pyrimidinyl, (un)substituted thiazolyl, (un)substituted oxazolyl, or (un)substituted pyridyl. More preferably B is an (un)substituted phenyl, (un)substituted pyridyl, or (un)substituted pyrimidinyl.
- 15

As defined herein both A or B may be optionally substituted, independently, with up to five, preferably up to three substituent groups, 20 hereinafter referred to as X and X₁ respectively.

- Examples of suitable X groups for A, when n is 1, include, cyano, amino, (C₁₋₆)alkanoylamino, mono- or di- (C₁₋₆)alkylamino, hydroxy, (C₁₋₆)alkoxy, substituted (C₁₋₆)alkoxy [also referred to as -O-R₁], 25 (C₁₋₆)alkylthio, (un)substituted heterocyclylthio, arylthio, (un)substituted sulphamoyl, (un)substituted carbamoyl, amidino, guanidino, nitro, halogen, carboxy and salts and esters thereof, (C₁₋₆)alkanoyloxy, arylcarbonyloxy, heterocyclylcarbonyloxy, and acyl groups.
- 30 Suitably optional substituents (X₁), for B when m is 1, include, for example, (C₁₋₆)alkyl, (poly)halo(C₁₋₆)alkyl, cyano, (un)substituted heterocyclyl, amino, (C₁₋₆)alkanoylamino, mono- or di-(C₁₋₆)alkylamino, substituted mono- or di-(C₁₋₆)alkylamino, [also referred to as -NR₂R₃], hydroxy, (C₁₋₆)alkoxy, substituted (C₁₋₆)alkoxy [also referred to as -O-R₁], (C₁₋₆)alkenoxy, hydroxy substituted (C₁₋₆)alkoxy, (un)substituted heterocyclylthio, arylthio, arylsulphinyl, arylsulphonyl, (C₁₋₆)alkylthio, 35 (C₁₋₆)alkylsulphinyl, (C₁₋₆)alkylsulphonyl, (un)substituted sulphamoyl, (un)substituted carbamoyl, amidino, guanidino, nitro, halogen, carboxy
 - 35

- 5 -

and salts and esters thereof, (C₁₋₆) alkylcarbonyloxy, arylcarbonyloxy, heterocyclcarbonyloxy, and acyl groups.

- When X or X₁ is a substituted alkoxy [-O-R₁], as hereinbefore defined,
- 5 the R₁ group may be a (C₂₋₆) alkenyl, (C₁₋₆) alkoxy alkyl, (poly)hydroxy (C₁₋₆) alkyl, (poly)halo(C₁₋₆) alkyl, substituted or unsubstituted heteroaryl (C₁₋₆) alkyl, substituted mono- or di- amino (C₁₋₆) alkyl, substituted or unsubstituted heterocycl (C₁₋₆) alkyl, or N-(C₁₋₆ alkyl)-N- heteroaryl-(C₁₋₆)alkyl.
- 10 As used herein, the term "(poly)" refers to the optional substitution of more than one, such as (poly)haloalkyl would allow for more than one halogen, independently on the alkyl moiety, i.e., -CF₃.
- 15 Preferably the R₁ group is a C₂₋₃ alkenyl, hydroxy C₁₋₆ alkyl, (C₁₋₆)alkoxy(C₁₋₆)alkyl, (poly)halo(C₁₋₆) alkyl, (un)substituted (C₁₋₆) alkyl heteroaryl, (un)substituted (C₁₋₆) alkyl heterocycl, or N-(C₁₋₆ alkyl)-N- pyridyl-(C₁₋₆)alkyl. Preferably the heteroaryl is a pyridyl, or furanyl moiety. Preferably the heterocycl is a piperidine group.
- 20 More preferably R₁ is ethenyl, 2-ethanol, 3-propanol, -CH₂-O-CH₃, CH₂-furanyl, CH₂-furan-2-yl-5-nitro; CF₃, N-methyl-N-2-pyridylaminoethyl, N-piperidinylethyl, or 4-pyridylmethyl.
- 25 When X₁ is NR₂R₃, the R₂ and R₃ moieties are independently a (C₁₋₆) alkyl group or one of R₂ or R₃ may be a hydroxy (C₁₋₆) alkyl group. Preferably, both R₂ and R₃ are (C₁₋₆) alkyl, more preferably methyl; or one of R₂ R₃ is methyl and the other 2-ethanol.
- 30 Preferably the X₁ substitutents are selected from hydroxy, substituted and unsubstituted (C₁₋₆)alkoxy, (C₁₋₆)alkyl, oxy(C₁₋₆)alkyl, cyano, chloro, fluoro, bromo, nitro, hydroxy(C₁₋₆)alkyl, (C₁₋₆)alkylthio, (C₁₋₆)alkylsulphinyl, (C₁₋₆) alkylsulphonyl, NR₂R₃, or (un)substituted heterocycl, or gem di(C₁₋₆)alkoxy(C₁₋₆)alkyl.
- 35 More preferably X₁ is methoxy, C(O)CH₃, methyl, cyano, chloro, fluoro, bromo, -CH(OCH₂CH₃)₂, nitro, -CH(O), N(CH₃)₂, SCH₃, S(O)CH₃, S(O)₂CH₃, -CH₂OH, piperidine, O-CF₃, hydroxy, ethenyoxy, 2-

- 6 -

hydroxyethoxy, N-(2-hydroxyethyl)-N-methylamino, 3-hydroxypropyloxy, azidoethoxy, N-methyl-N-pyridylaminoethoxy, piperidinylethoxy, pyridylmethoxy, nitrofuranyl methyloxy, or furanylmethyloxy.

- 5 For the optional substituent groups X and X₁ wherein their respective members are also referred to as (un)substituted group, the optional substituents for said groups are independently substituted up to five times, preferably up to three times, from the same group listed herein under the X₁ term. For example, (un)substituted carbamoyl would allow 10 the nitrogen atom to be mono- or di-substituted with a (C₁₋₆)alkyl moiety; the (un)substitued heterocyclic would allow, for example, a piperidine ring to be substituted by a (C₁₋₆)alkyl, or hydroxy moiety; an (un)substituted heteroaryl would allow for a furanyl ring to be substituted by a nitro group.
- 15 Preferred substituent groups (X₁) when B is an aryl group include, for example, halogen, cyano, (C₁₋₆)alkyl, hydroxy(C₁₋₆)-alkyl, oxo(C₁₋₆)alkyl, gem di(C₁₋₆)alkoxy(C₁₋₆)alkyl, (C₁₋₆)alkoxy, (C₂₋₆)alenoxy, hydroxy(C₁₋₆)alkoxy, (C₁₋₆)alkoxy(C₁₋₆)alkoxy, halo(C₁₋₆)alkyl, hydroxy, 20 amino, mono- or di-(C₁₋₆)alkylamino, acylamino, nitro, carboxy, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkoxycarbonyl(C₁₋₆)alkyl, (C₁₋₆)alkylcarbonyloxy, (C₁₋₆)alkylthio, (C₁₋₆)alkylsulphiny, (C₁₋₆)-alkylsulphonyl, sulphamoyl, mono- or di-(C₁₋₆)alkylsulphamoyl, carbamoyl, mono- or di-(C₁₋₆)alkylcarbamoyl and heterocyclyl.
- 25 Preferred substituents (X₁) when B is a heteroaryl group include, for example, halogen, (C₁₋₆)alkyl, (C₁₋₆)cycloalkyl, (C₁₋₆)alkoxy, hydroxy(C₁₋₆)alkoxy, halo(C₁₋₆)alkyl, hydroxy, amino, mono- or di-(C₁₋₆)alkylamino, N-hydroxy(C₁₋₆)alkyl N-(C₁₋₆)alkyl amino, carboxy, 30 (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkoxycarbonyl(C₁₋₆)alkyl, aryl, oxo, non-aromatic heterocyclyl, (C₁₋₆)alkylthio, (C₁₋₆)alkylsulphiny and (C₁₋₆)alkylsulphonyl.
- 35 Preferred substituent (X₁) when B is a heterocyclyl group include, for example, halogen, (C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, (C₁₋₆)alkoxy, hydroxy(C₁₋₆)alkoxy, halo(C₁₋₆)alkyl, hydroxy, amino, mono- or di-(C₁₋₆)alkylamino, carboxy, (C₁₋₆)alkoxycarbonyl, (C₁₋₆)alkoxycarbonyl(C₁₋₆)alkyl, aryl and oxo.

When a substituent group, preferably in the (B)_m term, has an acidic hydrogen arising from the presence in a heteroaryl ring of an NH moiety, for instance, when R⁰ is pyrazolyl, the hydrogen may be replaced by a (X or X₁) substituent as hereinbefore defined. Preferably the substituent is a (C₁₋₆) alkyl group.

As used herein, the term "alkyl" group or moiety referred to herein may be a straight or branched hydrocarbon chain, and may contain, for example, up to 12 carbon atoms, suitably up to 6 carbon atoms. The alkyl chain may be unsubstituted or substituted. In particular, the alkyl group or moiety may be an unsubstituted or substituted methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, isobutyl or tert-butyl group. Examples of suitable optional substituents for any such alkyl group or moiety include the above-listed substituents for the (A)_n term.

When used herein, the term 'aryl' includes, unless otherwise defined, phenyl or naphthyl.

When used herein, the term 'heterocyclyl' and 'heterocyclic' includes non-aromatic single or fused rings comprising up to four heteroatoms in each ring selected from oxygen, nitrogen and sulphur. Suitably, the heterocyclic ring comprises from 4 to 7, preferably from 5 to 6 ring atoms. A fused heterocyclic ring system may include aromatic carbocyclic and heteroaryl rings. Suitably the heterocyclic group is piperidinyl.

When used herein, the term 'heteroaryl' includes aromatic heterocyclic containing rings and ring systems as is commonly defined in the art, such as by Katritzky *et al.*, Handbook of Heterocyclic Chemistry, Pergamon Press, Oxford, England (1985). As defined therein, a heteroaromatic structure is based on the 6 π -electron system. These structures are related to and formally derived from benzene by successive replacement of one or two annular CH groups by trivalent or divalent heteroatom groups respectively. The overall pattern of filled bonding molecular orbitals is retained. Thus replacement of one CH group by O⁺, S⁺, or N gives the six-membered pyrylium, thiinium or pyridine systems, and replacement of two CH groups by O, S, or NH gives the five-membered furan, thiophene, or pyrrole. Multiple replacements are also possible with up to four

heteroatoms in five- and six-membered rings. Suitably the heteroaryl ring has 5 to 6 ring atoms in each ring. Preferred heteroaryl groups herein include, pyridyl, pyrimidinyl, furanyl, thienyl, thiazolyl, isoxazolyl, oxazolyl and pyrazolyl.

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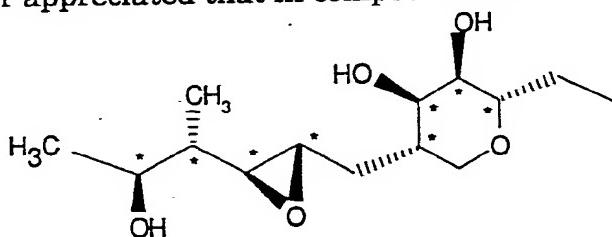
When used herein, the term "hydrocarbyl" may include groups having up to 18 carbon atoms, suitably up to 10 carbon atoms, conveniently up to 6 carbon atoms. Suitable groups include those listed under the $(A)_n$ term and the $(B)_m$ term groups which do not contain a heteroatom, i.e.

10 cycloalkyl, cycloalkenyl and aryl.

It will be appreciated that another aspect of the present invention is in the many variations which can result from the point of attachment of the respective heteroaryl rings, such as in the 2-pyridyl, 3-pyridyl or 4-pyridyl 15 moieties. Further where isomers of a heteroaryl exist, such as in a 1,3-pyrazolyl or 1,2-pyrazolyl, said isomers are also another aspect of the present invention.

When used herein, the term 'halogen' refers to fluorine, chlorine, bromine 20 or iodine. Preferably, the halogen is fluoro, chloro or bromo.

It will be further appreciated that in compounds of formula (I), the moiety:



will have the same relative and absolute stereochemistry at each of the 25 chiral centres (indicated by *) as that of corresponding moiety in mupirocin i.e. [2S, 3R, 4R, 5S] about the tetrahydropyran ring and [2S, 3S, 4S, 5S] in the 5-(2,3-epoxy-5-hydroxy-4-methylhexyl) sidechain of the tetrahydropyran ring.

30 The compounds of the present invention may exist in the forms shown in formulae (IA), (IB) or (IC), the three forms being in equilibrium. It will be appreciated that the compounds of formulae (IA), (IB), and (IC) are interrelated by keto-enol tautomerism, with formula (IA) representing the keto tautomer and formula (IB) and (IC) representing the two possible

enol tautomers. References hereinafter to 'formula (I)' encompass all three forms unless the context requires otherwise.

It will be appreciated that in compounds of formula (I), the group R⁰ may 5 contain one or more chiral centres. The present invention encompasses all such resultant isomeric possibilities.

- Since the compounds of formula (I) of the present invention are intended for use in pharmaceutical compositions, it will be understood that they are 10 each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate 15 compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.
- 20 When some of the compounds of this invention are allowed to crystallise, or are recrystallised, from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In 25 such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.
- 30 Examples of compounds within the scope of this invention include the following:

3R,4R-Dihydroxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)-but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

35 3R,4R-Dihydroxy-2S-(2,4-dioxo-4-phenyl-but-1-yl)-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

- 10 -

- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)but-1-yl]-5S-(2S,3S,epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 2S-[4-(4-Acetylphenyl)-2,4-dioxobut-1-yl]-3R,4R-dihydroxy-
5 5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[4-(4-dimethylaminophenyl)-2,4-dioxobut-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 10 3R,4R-Dihydroxy-2S-(2,4-dioxo-4-(furan-3-yl)but-1-yl]-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methylpyrazol-4-yl)-
but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-
15 tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(furan-2-yl)but-1-yl]5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 20 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-4-yl)but-1-yl]5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-3-yl)but-1-yl]5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
25
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-2-yl)but-1-yl]5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methylisoxazol-5-yl)-
but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-
30 hydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methoxyphenyl)but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
35
- 3R,4R-Dihydroxy-2S-[4-(4-cyanophenyl)-2,4-dioxobut-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

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- 3R,4R-Dihydroxy-2S-[4-(4-chlorophenyl)-2,4-dioxo-but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[4-(4-diethoxymethylphenyl)-2,4-dioxobut-1-yl]-
5 5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[4-(4-dioxo-4-(4-formylphenyl)-but-1-yl]-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 10 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran.
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-2-yl)but-1-yl]-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-3-yl)but-1-yl]-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrid-5-yl)-2,4-
20 dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-
hexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)but-1-yl]-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
25 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylsulphinylypyrid-5-yl)but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylsulphonylypyrid-5-yl)but-1-yl]-
30 5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-
epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 35 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-hydroxymethylfuran-2-yl)but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-nitrothien-4-yl)but-1-yl]-5S-(2S,3S-

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- epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[4-(2-bromopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-
epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 5 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-methoxyfuran-2-yl)but-1-yl]-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 10 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(piperidin-1-yl)-pyrimidin-5-yl)but-1-
yI]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methyl-2-methylthioimidazol-4-yl)-
but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 20 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxyphenyl)but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 25 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-
yI]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 30 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylsulphonyl-phenyl)-
but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 35 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-cyanophenyl)but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-hydroxyphenyl)but-1-yl]-5S-(2S,3S-
epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

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- 3R,4R Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 5 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethyloxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 10 3R,4R-Dihydroxy-2S-[4-(but-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 20 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 25 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-N-(2-hydroxyethyl)-N-methylaminopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 30 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(4-hydroxypiperidin-1-yl)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran;
- 35 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(3-hydroxyprop-1-oxy)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(furan-2-yl)hex-1(E)-en-6-yl]-5S-

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- (2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-hydropyran;
- 3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(4-methoxyphenyl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 5 3R,4R-Dihydroxy-2S-(3,5-dioxo-1-phenylhex-1-yn-6-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 10 3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrimidin-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-N-methyl-N-2-pyridylamino-ethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 20 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-piperidinylethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{4-pyridylmethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 25 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{5-nitrofuran-2-ylmethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 30 and
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{furan-2-ylmethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-6S-hydroxy-4S-methylhexyl)tetrahydropyran.

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Preferred compounds of the instant invention are:

- 3R,4R-Dihydroxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 5 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)-but-1-yl]-5S-(2S,3S,epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 10 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran;
- 15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 20 3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 25 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 30 3R,4R Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 35 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethyloxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran; and
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran.

35

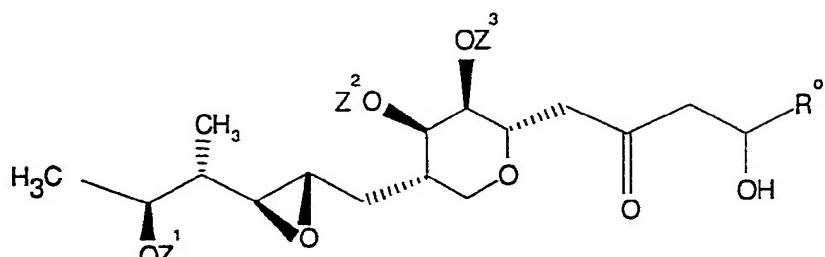
Compounds of the present invention may be prepared by methods known for the preparation of β -diketones. Some of these processes will be more

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appropriate than others.

Suitably, compounds of formula (I) may be prepared by a process which comprises treating a compound of formula (II):

5



(II)

10 in which Z¹, Z² and Z³ are the same or different and each is hydrogen or a hydroxyl-protecting group, and R^o is as hereinbefore defined;

with an oxidising agent which converts a β -hydroxyketone into a β -diketone;

15

and thereafter, and if necessary, removing any hydroxyl-protecting groups.

Suitably such oxidising agents include, for example, activated manganese dioxide, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), chromium trioxide, pyridinium dichromate, pyridinium chlorochromate, dimethylsulphoxide/trifluoroacetic anhydride, dimethylsulphoxide/oxalyl chloride, ruthenium tetroxide, and tetra-n-propylammonium perruthenate.

25

Suitably, the oxidation reaction is effected in an organic solvent such as, for example, dioxan, acetonitrile, tetrahydrofuran, ether, carbon tetrachloride, chloroform, dichloromethane, benzene or toluene and at a temperature which is preferably in the range from -20° to 100°C.

30

Preferably, the compounds of Formula (I) wherein (A)_n is an alkenyl or alkenyl moiety in which the double or triple bond is in a conjugated or non-conjugated system with the rest of the molecule are made according to

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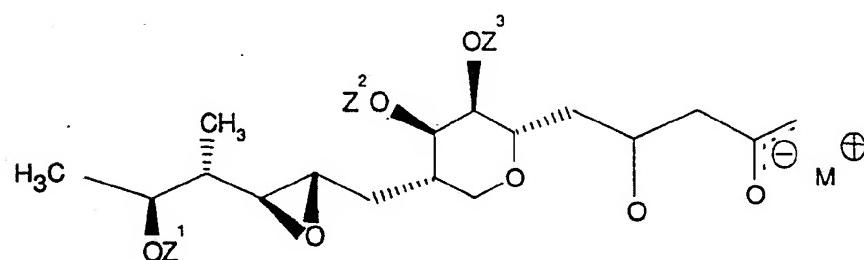
the process of Formula (II) as noted above. Alternatively, under carefully controlled conditions the process of Formula (VI) as hereinbelow defined, may also be used.

- 5 Compounds of formula (II) are novel and useful intermediates for the preparation of compounds of formula (I).

Accordingly, a further aspect of the invention also provides a compound of formula (II) as hereinbefore defined.

10

Compounds of formula (II) may be prepared by a process which comprises treating a compound of formula (III):



15

(III)

in which Z^1 , Z^2 and Z^3 are as hereinbefore defined and M^+ is a metal such as lithium, with an aldehyde of formula (IV):

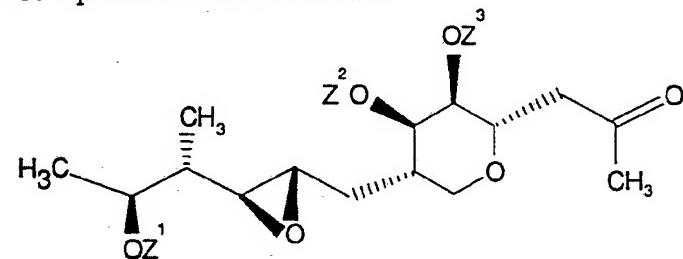
20

R^0CHO (IV)

in which R^0 is as hereinbefore defined and thereafter, and if necessary, removing any hydroxyl-protecting groups.

25

A compound of formula (III) may be obtained by treating a ketone compound of formula (V):



(V)

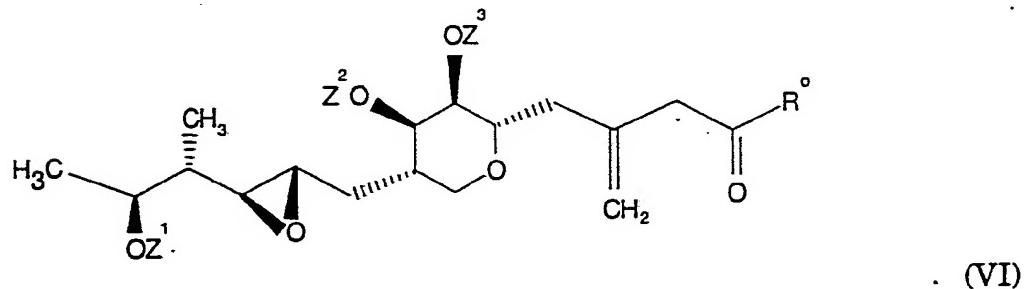
in which Z^1 , Z^2 and Z^3 are as hereinbefore defined, with a suitable enolising agent such as, for example, lithium diisopropylamide.

- 5 It will be appreciated that in practice, the compound of formula (III) may be generated *in situ*, prior to the treatment thereof with a compound of formula (IV).

- 10 The preparation of a compound of formula (V) is described in GB 1 587 58 (to Beecham Group plc).

In a further aspect, the present invention provides a second process for preparing a compound of formula (I) as hereinbefore defined, which process comprises treating a compound of formula (VI):

15



- 20 in which Z^1 , Z^2 , Z^3 and R^o are as hereinbefore defined, with a reagent capable of converting a terminal methylene-substituent to an oxo-substituent and thereafter, and if necessary, removing any hydroxyl-protecting groups.

- 25 Suitable reagents for effecting such a conversion include ozone and osmium tetroxide, each of which forms an intermediate which may then be converted to the compound of formula (I). Alternative reagents useful in the conversion herein may be found in Harrison *et al*, Compendium of Organic Synthetic Methods, Wiley-Interscience (1971).

- 30 Ozonolysis may be effected under conditions conventionally used for such a reaction. Thus the reaction may be effected at a low temperature, for instance about -70^o , in the presence of a suitable solvent such as dichloromethane. The intermediate ozonide thus formed may be

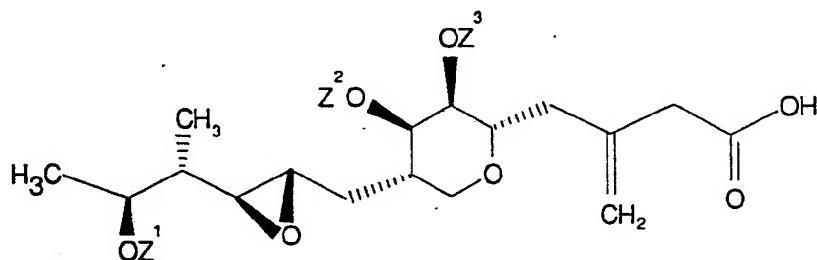
conveniently decomposed by an agent conventionally used for such a task, of which triphenyl phosphine is especially preferred.

Alternatively, the compound of formula (VI) may be treated with osmium tetroxide, according to the procedure described by V. Van Rheenen, R.C. Kelly and D.Y. Cha, Tetrahedron Lett, 1976, 1973. Preferably a catalytic quantity of osmium tetroxide is employed, in the presence of a tertiaryamine oxide catalyst such N-methylmorpholine N-oxide, in a solvent such as aqueous tetrahydrofuran, to give an intermediate 1,2-diol which may then be treated with an oxidising agent such as sodium periodate to give the compound of formula (VI).

Compounds of formula (VI) are novel and useful intermediates for preparing of compounds of formula (I).

Accordingly, a further aspect of the invention also provides a compound of formula (VI) as hereinbefore defined.

Suitably, compounds of formula (VI) may be prepared by a process which comprises treating the acid of formula (VII) or an activated derivative thereof:



(VII)

in which Z^1 , Z^2 and Z^3 are the same or different and each is hydrogen or a hydroxyl-protecting group,

with an organometallic reagent;
and thereafter, and if necessary, removing any hydroxyl-protecting groups.

Suitable organometallic reagents include:

- 5 (i) a Grignard reagent of the formula R^0MgX in which R^0 is as defined with respect to formula (I) and X represents chlorine, bromine or iodine, which reaction may optionally be carried out in the presence of copper(I) iodide as catalyst;
- 10 (ii) an organolithium reagent of formula R^0Li in which R^0 is as defined with respect to formula (I);
- 15 (iii) an organomanganese reagent of the formula R^0MnCl in which R^0 is as defined with respect to formula (I); and
- 20 (iv) an organocerium reagent $R^0Li-CeX_3$, in which R^0 is as defined with respect to formula (I) and X represents chlorine, bromine or iodine.

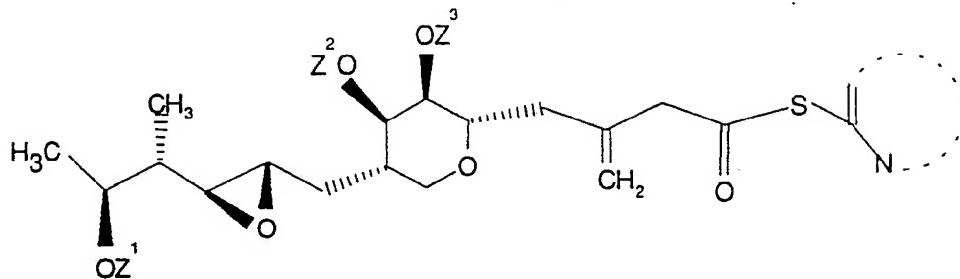
The reaction with the organometallic reagent may be conveniently carried out in an ethereal or hydrocarbon solvent, the choice of which is dependent upon the specific requirements of the organometallic reagent.

20 Preferably, the Grignard reagent is generated and used in diethyl ether or tetrahydrofuran.

The reaction is generally carried out in an inert atmosphere such as argon or nitrogen and at ambient temperature or below. The period for which the reaction is allowed to proceed depends upon the particular starting materials employed. The course of the reaction may be followed by conventional methods such as thin layer chromatography and the reaction may be terminated when an optimum quantity of product is present in the reaction mixture.

30 Suitable activated derivatives of the acid of formula (VII) include thio-esters of formula (VIII):

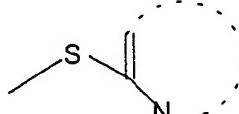
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(VIII)

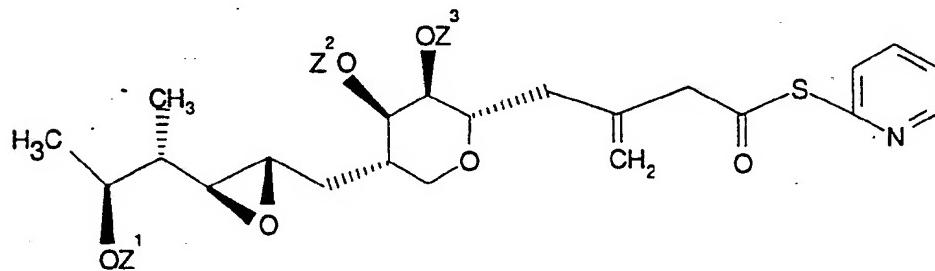
in which Z¹, Z² and Z³ are as hereinbefore defined and the moiety:

5



represents a 5- or 6-membered heterocyclic ring which may contain in addition to the nitrogen atom, one or two further heteroatoms selected from oxygen, nitrogen and sulphur and which may be substituted or fused
10 to a benzene ring which may itself be substituted.

Preferred thio-esters are of formula (VIIIa):



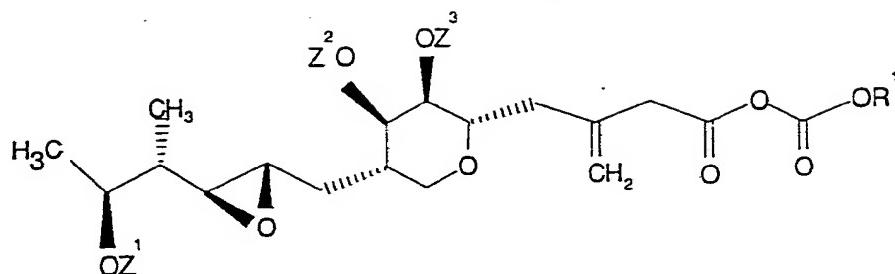
15

(VIIIa)

in which Z¹, Z² and Z³ are as hereinbefore defined.

Other suitable activated derivatives of the acid of formula (VII) include
20 mixed anhydrides of the formula (IX):

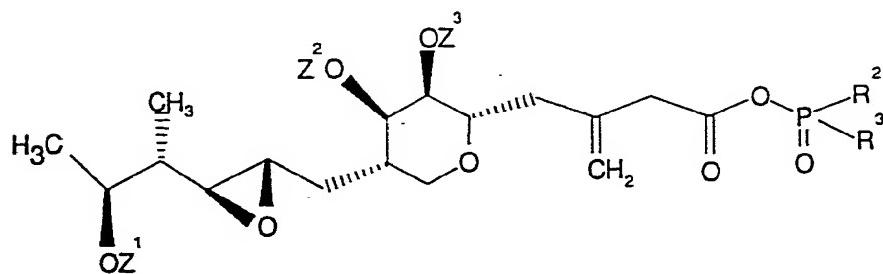
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(IX)

in which Z^1 , Z^2 , and Z^3 are as hereinbefore defined, and R^1 is
5 (C_{1-6})-alkyl;

and of the formula (X):

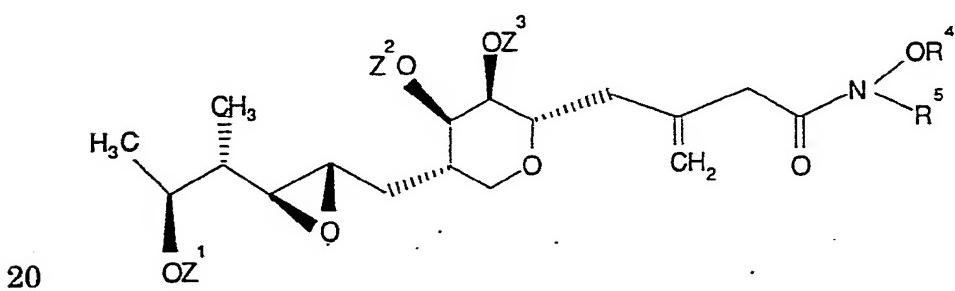


10

(X)

in which Z^1 , Z^2 , and Z^3 are as hereinbefore defined, and R^2 and R^3 are
the same or different and each denotes an aryl group, for instance phenyl,
15 or a (C_{1-6})-alkoxy group, for instance ethoxy.

Further suitable activated derivatives of the acid of formula (VII) include
amides of the formula (XI):



20

(XI)

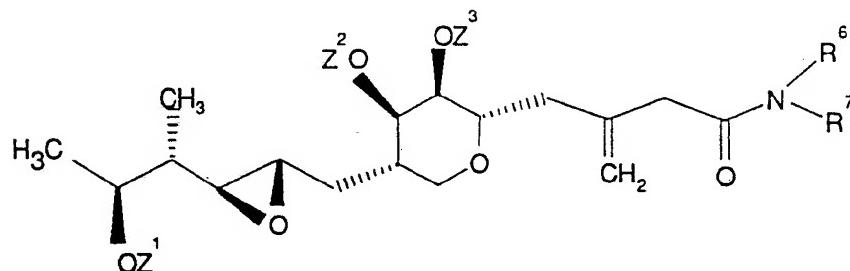
in which Z^1 , Z^2 and Z^3 are as hereinbefore defined, R^4 and R^5 are the

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same or different, and each is (C₁₋₆)alkyl, preferably methyl, or the substituents R⁴ and R⁵ form a (C₂₋₇)alkylene chain and;

amides of the formula (XII):

5



(XII)

- 10 in which Z¹, Z², and Z³ are as hereinbefore defined and R⁶ and R⁷, together with the nitrogen atom to which they are bonded, form an imidazolyl or triazolyl ring.

15 The reaction of an N-methoxy-N-methylamide compound with an organolithium or a Grignard reagent to form a ketone is described by Nahm and Weinreb in *Tetrahedron Lett.*, 1981, 3815. The reaction of an α,β-unsaturated acid or its imidazolyl derivative with a Grignard reagent is described in *Chem. Ber.*, 1965, 95 1284.

- 20 Suitably a thio-ester of formula (VIII) is treated with an organomanganese reagent of formula R⁰MnCl, as hereinbefore defined.

Suitably an amide of formula (XI) or (XII) is treated with an organolithium reagent of formula R⁰Li as hereinbefore defined:

- 25 Suitable organometallic reagents may be prepared according to conventional procedures.

30 Suitable organomanganese reagents of the formula R⁰MnCl may be conveniently prepared by addition of an organolithium reagent R⁰Li to a solution of manganese chloride and lithium chloride in dry THF, or a suspension of anhydrous manganese chloride in dry THF. An excess of R⁰MnCl is preferably employed. Alternatively, a Grignard reagent may

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be used in place of the organolithium reagent, to generate the organomanganese reagent R^0MnCl .

Other organomanganese reagents which may be used instead of R^0MnCl
5 include:

- (i) $(R^0)_3MnLi$ or $(R^0)_3MnMgX$ in which X is as hereinbefore defined,
as described in Synthetic Communications, 1979, 9, 639;
- 10 (ii) R^0MnI in ether; as described in Synthetic Communications, 1979, I,
639; and
- (iii) R^0MnBr in ether, as described in Tetrahedron Lett., 1976, 3155.

15 As in the case of R^0MnCl , the above organomanganese reagents may be prepared in situ when required.

Organocerium reagents may be generated in situ by treatment of an organolithium compound of the formula R^0Li , in which R^0 is as
20 hereinbefore defined, with cerium (III) halide, by analogy with the procedure described by Imamoto et al; J. Chem. Soc., Chem. Commun., 1982, 1042.

The activated derivatives of compounds of formula (VI) may be prepared
25 from the compounds of formula (VI) by standard methodology.

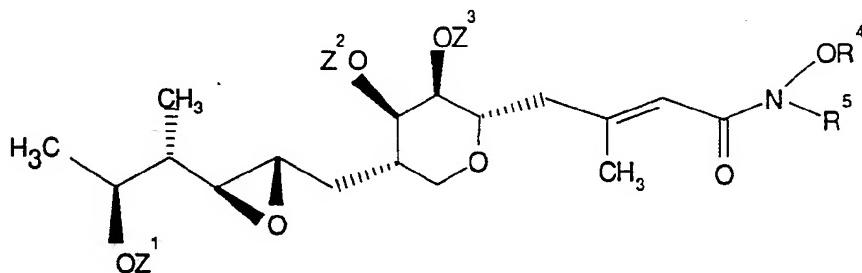
Compounds of formula (VII) may be obtained by treating the protected methylester of monic acid with a base such as lithium diisopropylamide, as described by Crimmin et al, J. Chem. Soc., Perkin Trans I, 1985, 549,
30 followed by ester hydrolysis.

Advantageously, a compound of formula (VI) may be prepared by treating a compound of formula (XI) in which R^4 and R^5 each is methyl with an organometallic reagent which is preferably an organolithium reagent of
35 the formula R^0Li .

Compounds of formula (XI) are novel and useful intermediates in the preparation of compounds of formula (VI).

Accordingly, a further aspect of the invention provides compounds of formula (XI) as hereinbefore defined.

- 5 Compounds of formula (XI) may also be obtained by a process which comprises treating a compound of formula (XIII):



10

(XIII)

- in which Z¹, Z², Z³, R⁴ and R⁵ are as hereinbefore defined, with a strong non-nucleophilic base such as, for example, lithium diisopropylamide, followed by quenching with a mild proton source such as ammonium chloride.

15

Compounds of formula (XIII) are novel and useful intermediates for the preparation of compounds of formula (XI).

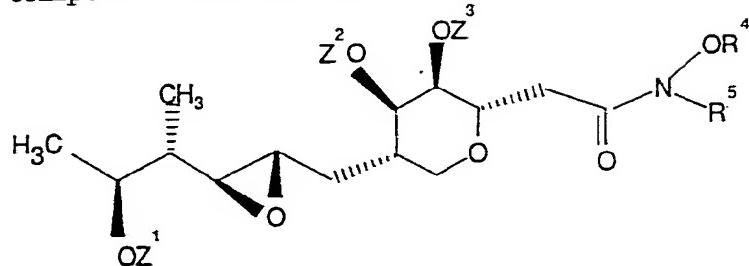
- 20 Accordingly, a further aspect of the invention provides a compound of formula (XIII) as hereinbefore defined.

- Compounds of formula (XIII) may be prepared from monic acid by initial conversion thereof to an activated derivative, for instance a mixed anhydride such as that formed with iso-butylchloroformate, followed by subsequent treatment with an amine HN(OR⁴)R⁵ in which R⁴ and R⁵ are as hereinbefore defined, or a salt thereof; under standard conditions, for instance, with dichloromethane as the reaction solvent, at about 0°C for 2h; and thereafter and if required, introducing any hydroxyl-protecting groups that may be subsequently required.

In a further aspect, the present invention provides a third process for preparing a compound of formula (I) which process comprises treating a

- 26 -

compound of formula (XIV):



(XIV)

- 5 in which Z^1 , Z^2 , Z^3 , R^4 and R^5 are as hereinbefore defined, with a compound of formula (XV):



(XV)

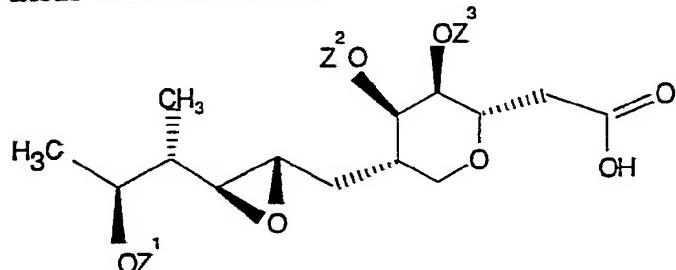
10

in which R^o is as hereinbefore defined and thereafter, and if necessary, removing any hydroxyl-protecting groups.

15 Compounds of formula (XIV) are novel and useful intermediates for the preparation of compounds of formula (I).

Accordingly, a further aspect of the invention provides a compound of formula (XIV) as hereinbefore defined.

20 Compounds of formula (XIV) may be prepared from the corresponding acids of formula (XVI):



(XVI)

25

in which Z^1 , Z^2 and Z^3 are as hereinbefore defined, by initial conversion thereof to an activated derivative, for instance a mixed anhydride such as that formed with iso-butylchloroformate, followed by subsequent

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treatment with an amine $\text{HN}(\text{OR}^4)\text{R}^5$, in which R^4 and R^5 are as hereinbefore defined, or a salt thereof, under standard conditions, for instance, with dichloromethane as the reaction solvent, at about 0°C for 2h.

- 5 Compounds of formula (XVI) are novel and useful intermediates for the preparation of compounds of formula (I).

Accordingly, a further aspect of the invention provides a compound of formula (XVI); as hereinbefore defined.

- 10 Compounds of formula (XVI) may be prepared from compounds of formula (V), as hereinbefore defined, and in which the hydroxyl groups are protected, preferably as a silyl ether, by initial conversion thereof to the enol form followed by ozonolysis and subsequent decomposition of the 15 intermediate ozonide using, for instance, dimethyl sulphide.

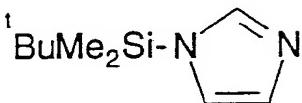
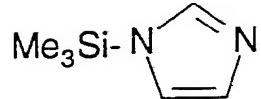
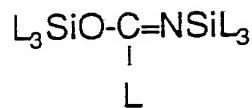
- Compounds of formula (I) may be obtained from other compounds of formula (I) by suitable manipulation of the substituents present in the group R^0 according to conventional methodology. For instance, an 20 alkylthio substituent may be converted to an alkyl sulphanyl or an alkylsulphonyl substituent by treatment thereof with a conventional oxidising agent such as m-chloroperbenzoic acid.

- When used herein, the term 'hydroxyl-protecting group' refers to any such 25 group known in the art which may be removed without disruption of the remainder of the molecule. Suitable hydroxyl-protecting groups include those described in 'Protective Groups in Organic Synthesis', T.W. Greene, Wiley-Interscience, New York 1981.

- 30 The hydroxyl groups of the compounds of formulae (II), (III), (V) to (XIV) and (XVI) may be protected at any stage of the above processes, using conventional methods. The hydroxyl-protecting group may be removed by methods known in the art, including enzymatic methods.

- 35 Particularly suitable hydroxyl-protecting groups are silyl groups since these are readily removed under mild conditions. Such groups are introduced using conventional silylating agents, including halosilanes and silazanes, of the formulae below:

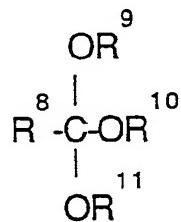
- 28 -



wherein Me denotes methyl and t Bu denotes t-butyl, Y is halogen and each group L is independently selected from hydrogen, (C₁₋₆)alkyl, (C₁₋₆)alkoxy, aryl or aryl(C₁₋₄)alkyl. A preferred silyating agent is

5 trimethylsilyl chloride. Particularly suitable protecting groups are trimethylsilyl, triethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl groups. Preferred protecting groups are trimethylsilyl groups because of their ease of removal.

10 The glycol function of the compounds of formulae (II), (III), (V) to (XIV) and (XVI) may be protected by forming a cyclic derivative using a compound of formula (XVII):

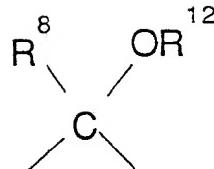


15

(XVII)

wherein R⁸ is hydrogen or (C₁₋₆)alkyl and each of R⁹, R¹⁰ and R¹¹ is (C₁₋₆)alkyl. In the cyclic derivative Z¹ and Z² together are a moiety:

- 29 -



in which R⁸ is as hereinbefore defined and R¹² is (C₁₋₆)alkyl.

Suitably R⁸ is hydrogen, methyl, ethyl, n- or iso-propyl; most suitably it is
5 hydrogen. The groups R⁹, R¹⁰ and R¹¹ are suitably methyl, ethyl, n- or
iso-propyl, or n-, iso-, sec- or t-butyl; most suitably methyl.

Similarly the hydroxyl groups of a compound of formula (I) may be
protected prior to conversion to a further compound of formula (I) as
10 described above.

In each case the hydroxyl-protecting groups described above may be removed by mild acid hydrolysis followed by alkaline hydrolysis, for instance, as described by J.P. Clayton, K. Luk and N.H. Rogers, in
15 'Chemistry of Pseudomonic Acid, Part II', J.C.S. Perkin Trans. I, 1979,
308.

The compounds of this invention are useful in therapy, in particular for the treatment of bacterial and mycoplasma-induced infections in
20 non-human and human animals, such as the treatment of respiratory tract infections, otitis, meningitis, skin and soft tissue infections in human animals, mastitis in cattle, and respiratory infections in non-human animals such as pigs and cattle.

25 The compounds of this invention are active against both Gram negative and Gram positive organisms, including Haemophilus, for instance H.influenzae Q1; Branhamella, for instance B.Catarrhalis 1502; Streptococci, for instance S.pyogenes CN10 and S.pneumonia PU7; and Staphylococci, for instance S.aureus Oxford, Legionella, for instance L.pneumophila; and against mycoplasma. In addition, compounds of the present invention are active against Staphylococci organisms such as S.aureus and S.epidermidis which are resistant, including multiply resistant, to other anti-bacterial agents, for instance macrolides; aminoglycosides; lincosamides; and β-lactams, such as, for example methicillin.

- 30 -

The compounds of this invention are also active against mycoplasma-induced infection, in particular Mycoplasma fermentans, which has been implicated as a co-factor in the pathogenesis of AIDS.

5 Accordingly in a further aspect, the present invention provides a method of treating humans infected with M. fermentans, in particular humans also infected with HIV, which method comprises treating humans in need of such therapy with an anti-mycoplasmal effective amount of a compound of formula (II).

10 This invention also provides a pharmaceutical or veterinary composition which comprises a compound of formula (I) (hereinafter referred to as the 'drug') together with a pharmaceutically or veterinarily acceptable carrier or excipient.

15 The compositions may be formulated for administration by any route, for instance, by topical, parenteral or oral administration and would depend on the disease being treated. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, 20 such as oral, topical or sterile parenteral suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or 25 polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in 30 normal pharmaceutical practice

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable 35 vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous

vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

5

For topical application to the skin the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics and

10 cosmetics, such as 'Harry's Cosmeticology' published by Longman, and the British Pharmacopoeia.

Suppositories will contain conventional suppository bases, e.g. cocoa-butters or other glyceride.

15

For parenteral administration, fluid unit dosage forms are prepared utilizing the drug and a sterile vehicle. The drug, depending on the vehicle and concentration used, can be suspended in the vehicle.

Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability thereof the composition may be frozen after filling into the vial and water removed under vacuum. The dry lyophilized powder is then sealed in the vial. The drug can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the drug.

30 For topical application to the ear, the drug may be made up into a suspension in a suitable liquid carrier, such as water, glycerol, diluted ethanol, propylene glycol, polyethylene glycol or fixed oils.

35 For topical application to the eye, the drug is formulated as a suspension in a suitable, sterile aqueous or non-aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edetate; preservatives including bactericidal and fungicidal agents, such as phenylmercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

The dosage employed for compositions administered topically will, of course, depend on the size of the area being treated. For the ears and eyes each dose will typically be in the range from 10 to 100 mg of the drug.

5

Veterinary compositions for intramammary treatment of mammary disorders in animals, especially bovine mastitis, will generally contain a suspension of the drug in an oily vehicle.

- 10 The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the drug, depending on the method of administration. Where the compositions are in unit dose form, each dosage unit will preferably contain from 50-500 mg of the drug. The dosage as employed for adult human treatment will preferably range from
15 100 mg to 3 g, per day, for instance 250 mg to 2 g of the drug per day, depending on the route and frequency of administration.

- 20 Alternatively, the drug may be administered to non-human animals as part of the total dietary intake. In this case the amount of drug employed may be less than 1% by weight of the diet and in preferably no more than 0.5% by weight. The diet for animals may consist of normal foodstuffs to which the drug may be added or the drug may be included in a premix for admixture with the foodstuff. A suitable method of administration of the drug to a non-human animal is to add it to the non-human animal's
25 drinking water. In this case a concentration of the drug in the drinking water of about 5-500 µg/ml, for example 5-200 µg/ml, is suitable.

- 30 The present invention further provides a method for treating the human or non-human animal which method comprises administering a compound of formula (I) as hereinbefore defined, to a human or non-human animal in need of such therapy.

Alternatively, a pharmaceutical composition as hereinbefore described may be employed in the treatment.

35

In particular aspects of the treatment, there are provided methods for treating bacterial infections and mycoplasma-induced infections of human or non-human animals, especially respiratory infections in human or

- 33 -

non-human animals.

The present invention also provides a compound of formula (I) as hereinbefore defined for use in therapy.

5

The present invention also provides a compound of formula (I) as hereinbefore defined for use in the manufacture of a medicament for anti-bacterial therapy or mycoplasma-induced infections.

- 10 The following Examples illustrate the invention, but are not intended to limit the scope in any way.

The Examples hereinafter are named according to the IUPAC convention. For the H nmr data, however, the numbering system is derived from

- 15 monic acid viz:

Preparation of N-methoxy-N-methyl 6,7,13-tris(trimethylsilyl) monamide

N,N-dimethyl hydroxylamine hydrochloride (1.95grams (hereinafter g.),

- 20 20milimoles (hereinafter mmoles)) was dissolved in dichloromethane/aqueous sodium hydroxide (20milliters (hereinafter ml:10ml, 2.5Molar (hereinafter M)). The aqueous layer was re- extracted with dichloromethane (10ml) and the combined organic layers washed with saturated brine (5ml). The organic layer was dried ($MgSO_4$) and 25 added to monic acid isobutyl carbonic anhydride (10mmol)*. After stirring at 20°C for 1 hour (hereinafter h) the reaction mixture was diluted with dichloromethane and washed with saturated aqueous sodium hydrogen chloride and brine. The combined aqueous solutions were extracted with ethyl acetate, and the combined organic solutions dried ($MgSO_4$) and 30 concentrated to give the amide, 3.0g.

This was taken up in tetrahydrofuran (50ml) and treated with triethylamine (8.4ml, 60mmol) and chlorotrimethyl silane (6.3ml, 50mmol). After 10 minutes a catalytic amount of 4-DMAP was added.

35

After 2h at room temperature the reaction was diluted with diethyl ether, filtered, and the filtrate evaporated. The residue was taken up in hexane, refiltered, and washed with water and brine. After drying and

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evaporation the residue was taken up in hexane (20ml) and allowed to crystallise at 0 to -20°C, to give the required product as a colourless crystalline solid, 34.0g, 50%, mp 78-79°C.

- 5 *Monic acid isobutyl carbonic anhydride was obtained by treating monic acid with iso-butylchloroformate and triethylamine in tetrahydrofuran at from -5 to 20°C for about 30 min.

Example 1

10

3R,4R-Dihydroxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

15

a) Deconjugation of N-Methoxy-N-methyl-6,7,13-tristrimethylsilylmonamide

20

A solution of N-methoxy-N-methyl-6,7,13-tristrimethylsilylmonamide (1.2g, 2mmol) in dry THF (20ml) under argon at -70°C was sequentially treated with diisopropylamine (0.03ml, 0.2mmol) and a solution of t-butyllithium (1.7M, 1.4ml, 2.4mmol) in hexane. After 30min the reaction mixture was quenched with saturated ammonium chloride. Ethyl acetate was added and the organic phase was washed with water, brine, then dried and evaporated to give a 4:1 mixture of the deconjugated⁺ and conjugated* monamides in quantitative yield. δ_H (CDCl₃) inter alia 4.93 (4/5H, s, 15-H⁺), 5.03 (4/5H, s, 15-H⁺) 6.18 (1/5H, s, 2-H^{*}).

30

b) 2-[3R,4R-Bistrimethylsilyloxy-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-2S-yl]methylprop-2-ene-1-yl 4-methoxyphenyl ketone

35

A solution of p-bromoanisole (0.75ml, 6mmol) in THF (20ml) at -70°C under argon was treated with a solution of n-butyllithium (1.5M, 4ml, 6mmol) in hexane. After 30min the mixture was treated with a solution of the mixture from 1a (1.2g, 2mmol) in THF (5ml). After a further 30min saturated ammonium chloride was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried (MgSO₄), evaporated and chromatographed on silica eluting with ethyl

- 35 -

acetate/hexane mixtures to give material containing the title compound (543mg); δ_H ($CDCl_3$) *inter alia* 0.93 (3H, d, J 6.9Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 3.87 (3H, s, Ar-OMe), 4.89 (1H, s, 15-H), 5.06 (1H, s, 15-H), 6.92 (2H, d, J 8.4Hz, 3',5'-H₂), 7.97 (2H, d, J 8.7Hz, 2',6'-H₂).

5

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydrofuran

10 A solution of the ketone from 1b (630mg, 0.8mmol) in dichloromethane (25ml) at -70°C was ozonolysed until a blue colour persisted. Argon was then passed through the mixture. Triphenylphosphine (124gmg 0.47mmol) was added and the mixture warmed to room temperature. The mixture was evaporated to low volume and chromatographed on silica

15 eluting with ethyl acetate/hexane mixtures to give the title compound (370mg, 70%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.86 (3H, s, OMe), 6.20 (1H, s, 2-H), 6.93 (2H, d, J 8.7Hz, 3',5'-H₂), 7.95 (2H, d, J 8.7Hz, 2',6'-Hz). The 1H spectrum indicated that the title compound was essentially in the enolic form.

20

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxyphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

25 A solution of the ketone from 1c (360mg, 0.54mmol) in methanol (10ml) was treated with dimethylaminopyridine dihydrochloride (3mg). After 30min the reaction mixture was diluted with dichloromethane, washed with sodium hydrogen carbonate solution, dried and evaporated.

Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title compound (175mg, 74%); ν_{max} (KBr) 3435, 1603cm⁻¹; λ_{max} (EtOH) 324nm (ϵ_m 18,430); δ_H ($CDCl_3$) *inter alia* 0.93 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.1Hz, 14-H₃), 3.86 (3H, s, Ar-OMe), 6.20 (1H, s, 2-H), 6.92 (2H, d, J 9.8Hz, 3',5'-H₂), 7.87 (2H, d, J 9.8Hz, 2',6'-H₂). δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.7 (C-9), 39.7 (C-8), 42.5 (C-4), 42.8 (C-12), 55.5 (OMe), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 69.1 (C-6), 70.3 (C-13), 71.3 (C-7), 73.9 (C-5), 96.5 (C-2), 114.0 (C-3'5'), 126.9 (C-1'), 129.3 (C-2',6'), 163.3 (C-4'), 183.0 (C-3), 193.1 (C-1). M/Z (FAB) MH^\pm 437. The 1H nmr spectrum indicated that the title compound

was essentially in the enolic form.

Example 2

5 3R,4R-Dihydroxy-2S-(2,4-dioxo-4-phenyl-but-1-yl)-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-[3R,4R-Bistrimethylsilyloxy-5S-(2S,3S-epoxy-5S-
trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-2S-
10 yl]methylprop-2-en-1-yl phenyl ketone

A solution of the products from 1a (600mg, 1mmol) in THF (20ml) under argon at -70°C was treated with a solution of phenyllithium in ether (2M, 1.5ml, 3mmol). After 30min the reaction was worked up as in 1b to give 15 material containing the title compound (300mg); δ_H (CDCl₃) *inter alia* 0.89 (3H, d, J 7.1Hz), 1.19 (3H, d, J 6.3Hz, 14-H₃), 4.91 (1H, s, 15-H), 5.08 (1H, s, 15-H), 7.40-7.60 (3H, m), 7.44-8.05 (2H, m).

b) 3R,4R-Bistrimethylsilyloxy-2S-(2,4-dioxo-4-phenyl-
20 but-1-yl)-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-
methylhexyl)tetrahydropyran

The material from 2a (300mg, 0.47mmol) was converted to the title 25 compound (182mg, 61%) using the method described in 1c. δ_H (CDCl₃) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 6.27 (1H, s, 2-H), 7.43-7.60 (3H, m), 7.82-7.95 (2H, m). The ¹H spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-(2,4-dioxo-4-phenyl-but-1-yl)-
30 5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 1d, the ketone from 2b (180mg, 0.28mmol) was deprotected to give the title compound (53mg, 47%); ν_{max} (KBr) 3422, 1609, 1570cm⁻¹; λ_{max} (EtOH) 312nm (ε_m 13,620), 248 (5140); δ_H (CDCl₃), *inter alia* 1.06 (3H, d, J 6.9Hz, 17-H₃), 1.29 (3H, d, J 6.2Hz, 35 14-H₃), 6.28 (1H, s, 2-H), 7.36-7.64 (3H, m), 7.83-7.98 (2h, m); δ_C (CDCl₃) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.6 (C-8), 42.8 (C-4), 42.8 (C-12), 55.7 (C-10), 61.3 (C-11), 65.7 (C-16), 69.0 (C-13), 71.3 (C-7), 73.8 (C-5), 97.5

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(C-2), 127.1 (C-3'5'), 128.7 (C-2',6'), 132.6 (C-4'), 134.3 (C-1'), 182.3 (C-3), 196.0 (C-1); (Found: M^+ 406.1991. $C_{22}H_{30}O_7$ requires M 406.1992). The 1H spectrum indicated that the title compound was essentially in the enolic form.

5

Example 3

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

10

a) 2-[3R,4R-Bistrimethylsilyloxy-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-2S-yl]methylprop-2-ene-1-yl 2-methoxy pyrid-5-yl ketone

15

Using the method described in 1b and on the same scale, 2-methoxy-5-bromopyridine (1.13g, 6mmol) was reacted to give material containing the title compound (470mg); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.00 (3H, s, OMe), 4.90 (1H, s, 15-H), 15.08 (1H, s, 15-H), 6.77 (1H, d, J 8.8Hz, 3'-H), 8.16 (1H, dd, J 2.3, 8.6Hz, 4'-H), 8.82 (1H, d, J 2.2Hz, 6'-H).

20

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

25

Using the method described in 1c, the material from 3a (470mg, 0.71mmol) was converted to the title compound (330mg, 70%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 4.00 (3H, s, OMe), k6.18 (1H, s, 2-H), 6.79 (1H, d, J 8.7Hz, 3'-H), 8.06 (1H, dd, J 2.3, 8.7Hz, 4'-H), 8.72 (1H, d, J 2.7Hz, 6'-H). The 1H spectrum indicated that the title compound was essentially in the enolic form.

30

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

35

Using the method described in 1d, the material from 3b was deprotected to give the title compound (100mg, 46%); ν_{max} (KBr) 3503, 3428, 1603,

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1494cm⁻¹; λ_{max} (EtOH) 315.5nm (ϵ_m 17,120); δ_H (CDCl₃) *inter alia* 0.93 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 4.00 (3H, s, OMe), 6.19 (1H, s, 2-H), 6.80 (1H, d, J 9.8Hz, 3'-H), 8.05 (1H, dd, J 2.4, 9.8Hz, 4'-H), 8.72 (1H, d, J 2.4Hz, 6'-H); δ_C (CDCl₃) 12.7 (C-17), 20.8 (C-14), 31.7 (C-9), 39.7 (C-8), 42.2 (C-4), 42.9 (C-12), 54.3 (C-10), 55.7 (C-11), 61.3 (OMe), 65.7 (C-16), 69.0 (C-6), 70.3 (C-13), 71.4 (C-7), 73.9 (C-5), 96.8 (C-2), 111.0 (C-3'), 124.0 (C-5'), 137.2 (C-4'), 147.6 (C-6'), 166.7 (C-2'), 181.9 (C-3), 194.0 (C-1); (Found: M⁺ 437.2048. C₂₂H₃₁NO₈ requires M⁺ 437.2050).

10

Example 4

2S-[4-(4-Acetylphenyl)-2,4-dioxobut-1-yl]-3R,4R-dihydroxy-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

To a solution of the trimethylsilylenol ether of p-bromoacetophenone (1.63g, 6mmol) in THF (20ml) under argon at -70°C was added dropwise a solution of n-butyllithium (1.5M, 4ml, 6mmol) in hexane. After 30min a solution of the mixture from 1a (1.2g, 2mmol) in THF (5ml) was added. After 30min saturated ammonium chloride was added and the mixture extracted with ethyl acetate. The organic phase was washed with brine, dried and evaporated. The residue was filtered through silica eluting with 20% (v/v) ethyl acetate/hexane. The filtrate was evaporated then dissolved in methanol (20ml) and treated with dimethylaminopyridine dihydrochloride (3mg). After 20min the mixture was diluted with ethyl acetate washed with sodium hydrogen carbonate, brine then dried and evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave material (330mg) which was a 2:1 mixture of deconjugated* and conjugate⁺ ketones [δ_H (CDCl₃) 5.00 (2/3H, s, 15-H*), 5.18 (2/3H, s, 15-H*), 6.83 (1/3H, s, 2-H⁺)].

This material was dissolved in dichloromethane (30ml) and ozonolysed at -70°C until a green/blue colour was obtained. Argon was then passed through the solution. Triphenylphosphine (194mg, 0.74mmol) was added and the mixture warmed to room temperature. Evaporation to low volume followed by chromatography on silica eluting with

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- dichloromethane/methanol mixtures gave the title compound (106mg);
 ν_{max} (KBr) 3436, 1684, 1603cm⁻¹; λ_{max} (EtOH) 256nm (E_m 8,550), 324.5
(11,750); δ_{H} (CDCl₃) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J
6.3Hz, 14-H₃), 2.65 (3H, s, COMe), 6.31 (1H, s, 2-H), 7.96 and 8.02 (4H,
5 ABq, J 8.5Hz); δ_{C} (CDCl₃) 12.7 (C-17), 20.8 (C-14), 26.8 (COMe), 31.6
(C-9), 39.7 (C-8), 42.8 (C-12), 43.0 (C-4), 55.6 (C-10), 61.2 (C-11), 65.5
(C-16), 69.0 (C-6), 70.3 (C-13), 71.3 (C-7), 73.9 (C-5), 98.3 (C-2), 127.2
(C-3'5'), 128.6 (C-2',6'), 138.3 (C-1'), 139.6 (C-4'), 179.8 (C-3), 197.5 (C-1),
197.6 (COMe); (Found: M⁺ 448.2106. C₂₄H₃₂O₈ requires M 448.2097).
10 The ¹H spectrum indicated that the title compound was essentially in the
enolic form.

Example 5

- 15 3R,4R-Dihydroxy-2S-[4-(4-dimethylaminophenyl)-2,4-
dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-
tetrahydropyran

- 20 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-dimethylamino-
phenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-
trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

- A solution of diisopropylamine (0.48ml, 3.36mmol) in dry THF (25ml)
under argon at -30°C was treated dropwise with a solution of
25 n-butyllithium (1.5M, 2.24ml, 3.36mmol) in hexane. After 15min the
mixture was cooled to -70°C and treated dropwise over 5min with a
solution of tristrimethylsilylmonone (1.45g, 2.8mmol) in THF (7ml). After
1 hour the mixture was treated with a solution of
p-dimethylaminobenzaldehyde (447mg, 3.2mmol) in THF (2ml). After a
30 further hour saturated ammonium chloride was added. The mixture was
extracted with ethyl acetate and the organic phase washed with brine,
then dried and evaporated. Chromatography on silica eluting with ethyl
acetate/hexane mixtures gave the title compound (300mg); δ_{H} (CDCl₃)
inter alia 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 2.94
35 (6H, s, NMe₂), 4.06-4.19 (1H, m, 5-H), 5.05-5.14 (1H, m, 1-H), 6.65-6.86
(2H, m, 2',6'-H₂), 7.25 (2H, d, J 6.5Hz, 3'5'-H₂).

- b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-dimethylamino-

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phenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-tri-
methylsilyloxy-4S-methylhexyl)tetrahydropyran

A solution of the product from 5a (300mg, 0.45mmol) in dioxan (15ml) was
5 treated with 2,3-dichloro-5,6-dicyanobenzoquinone (102mg, 0.45mmol). After 5min the mixture was diluted with dichloromethane, filtered through Kieselguhr, washing with dichloromethane, and the filtrate evaporated. Chromatography on silica eluting with ethyl acetate/hexane mixtures gave the title compound
10 (250mg, 83%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 3.06 (6H, s, -NMe₂), 6.17 (1H, s, 2-H), 6.68 (2H, d, J 9.0Hz, 3'5'-H₂), 7.82 (2H, d, J 9.0Hz, 2',6'-H₂). The ¹H spectrum indicated that the title compound was essentially in the enolic form.

15 c) 3R,4R-Dihydroxy-2S-[4-(4-dimethylaminophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

A solution of the product of 5b (100mg, 0.15mmol) in THF (5ml) was
20 treated with 0.4M HCl (1ml). After 2min saturated sodium hydrogen carbonate solution (1ml) was added. The mixture was then extracted with ethyl acetate and the organic phase washed with brine, dried and evaporated. Chromatography on silica eluting dichloromethane/methanol mixtures gave the title compound (64mg, 95%); ν_{max} (KBr) 3424, 1715, 1597, 1524cm⁻¹; λ_{max} (EtOH) 370nm (E_m 29,750); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.07 (6H, s, -NMe₂), 6.16 (1H, s, 2-H), 6.64 (2H, d, J 9.0Hz, 3',5'-H₂), 7.82 (2H, d, J 9.0Hz, 2',6'-H₂); δ_C ($CDCl_3$) 12.7 (C-17), 20.7 (C-14), 31.7 (C-9), 39.6 (C-8), 39.7 (NMe₂), 42.5 (C-4), 42.6 (C-12), 55.6 (C-10), 61.3 (C-11), 65.6 (C-16), 69.3 (C-6), 70.3 (C-13), 71.3 (C-7), 74.0 (C-5), 95.6 (C-2), 111.1 (C-3',5'), 121.1 (C-1'), 129.3 (C-2',6), 153.4 (C-4'), 183.8 (C-3), 192.1 (C-1); (Found: M⁺, 449.2423. C₂₄H₃₅NO₇ requires M 449.2414).

Example 6

35 3R,4R-Dihydroxy-2S-(2,4-dioxo-4-(furan-3-yl)but-1-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

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- a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(furan-3-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran
- 5 Using the method described in 5a and on the same scale, furan-3-carboxaldehyde (0.28ml, 3.2mmol) was reacted to give the title compound (1.3g, 75%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.07-4.18 (1H, m, 5-H), 5.05-5.18 (1H, m, 1-H), 6.38-6.42 (1H, m, 4'-H), 7.35-7.44 (2H, m, 2',5'-H₂).
- 10 b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(furan-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran
- 15 The product from 6a (650mg) in benzene (30ml) was treated with manganese dioxide (1.76g) and refluxed with provision for azeotropic removal of water (Dean and Stark apparatus containing molecular sieves 4A) for 4 hours. The mixture was diluted with dioxan filtered through Kieselguhr, washing pad well with dioxan and evaporated.
- 20 Chromatography on silica eluting ethyl acetate/hexane mixtures gave the title compound (267mg, 41%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 5.92 (1H, s, 2-H), 6.70 (1H, d, J 1.2Hz, 4'-H), 7.45 (1H, m, 5'-H), and 7.99 (1H, s, 2'-H). The 1H spectrum indicated that the title compound was essentially in the enolic form.
- 25 c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(furan-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran
- 30 Using the method described in 5c, the product from 6b (200mg, 0.33mmol) was deprotected to give the title compound (120mg, 93%); ν_{max} (KBr) 3427, 1718, 1620, 1509cm⁻¹; λ_{max} (EtOH) 303.5nm (E_m 11,075); δ_H ($CDCl_3$) *inter alia* 0.93 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 5.93 (1H, s, 2-H), 6.69 (1H, d, J 1.6Hz, 4'-H), 7.46 (1H, s, with further fine coupling, 5'-H), 8.02 (1H, bs, 2'-H); δ_C ($CDCl_3$) 12.5 (C-17), 20.6 (C-14), 31.4 (C-9), 39.4 (C-8), 41.9 (C-4), 42.6 (C-12), 55.5 (C-10), 61.1 (C-11), 65.4 (C-16), 68.5 (C-6), 70.1 (C-13), 71.1 (C-7), 73.6 (C-5), 98.1 (C-2), 107.8 (C-2'), 123.8 (C-3'), 144.1 (C-4'), 145.6 (C-3'), 178.3 (C-3), 188.1

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(C-1); M/Z 396 (M^+ , 100%) and 95 (100). (Found M^+ 396.1788; $C_{20}H_{28}O_8$ requires M 396.1784). The 1H nmr spectrum indicated that the material was essentially in enolic form.

5 Example 7

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methylpyrazol-4-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

10

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(1-methylpyrazol-4-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

15

Using the method described in 5a, and on the same scale, 1-methylpyrazole-4-carboxaldehyde (352mg, 3.2mmol) was reacted to give the title compound (1.25g, 71%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.87 (3H, s, 1'-Me), 4.07-4.17 (1H, m, 5-H), 5.12-5.22 (1H, m 1-H), 7.36 (1H, s, 5'-H), 7.43 (1H, s, 3'-H).

20

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(1-methylpyrazol-4-yl)-but-1-yl]5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

25

Using the method described in 6b, the product from 7a (450mg, 0.7mmol) in benzene (15ml) was reacted with manganese dioxide (1.25g) for 1 1/2 hours to give the title compound (260mg, 58%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 3.94 (3H, s, NMe), 5.92 (1H, s, 2-H), 7.86 (2H, bs, 3',5'-H₂). The 1H nmr spectrum indicated that the title compound was essentially in the enolic form.

30

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methylpyrazol-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

35

Using the method described in 5c, the product from 7b (250mg, 0.4mmol) was deprotected to give the title compound (125mg, 76%); ν_{max} (KBr) 3424, 1718, 1617, 1546cm⁻¹; λ_{max} (EtOH) 308nm (ϵ_m 10,030); δ_H

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(CDCl₃) inter alia 0.94 (3H, d, J 7.1Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 3.94 (3H, s, NMe), 5.94 (1H, s, 2-H), 7.87 (2H, s, 3',5'-H₂); δ C (CDCl₃); 12.7 (C-17), 20.7 (C-14), 31.6 (C-9), 39.3 (C-8), 39.6 (1'-Me), 41.5 (C-4), 42.8 (C-12), 55.6 (C-10), 61.1 (C-11), 65.5 (C-16), 68.9 (C-6), 70.3 (C-13), 71.2 (C-7), 73.9 (C-5), 97.6 (C-2), 120.3 (C-4'), 131.7 (C-3'), 139.3 (C-5'), 179.6 (C-3), 191.5 (C-1); MZ (FAB) MNa \pm 433, MH \pm 411. The ¹H spectrum indicated that the title compound was essentially in the enolic form. Extra signals were observed in the ¹³C nmr spectrum which were identified as being from the presence of a small amount of the diketone form.

Example 8

15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(furan-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(furan-2-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 5a, and on the same scale, furan-2-carboxaldehyde (0.28ml, 3.36mmol) was reacted to give the title compound (1.196g, 69%); δ H (CDCl₃) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 4.10-4.22 (1H, m, 5-H), 5.15-5.22 (1H, m, 1-H), 6.27 (1H, m, 3'-H), 6.33-6.35 (1H, m, 4'-H), and 7.37 (1H, m, 5'-H); m/z 614 (M $^+$, 1%) and 117 (100). (Found: M $^+$, 614.3136. C₂₉H₅₄O₈Si₃ requires M, 614.3127).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(furan-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

30 Using the method described in 6b, the product from 8a (1.176g, 1.9mmol) in benzene (40ml) was reacted with manganese dioxide (4.3g) for 1 1/2 hours to give the title compound (0.601g, 51%); δ H (CDCl₃) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 6.17 (1H, s, 2-H), 6.54 (1H, dd, 3.6 and 1.7Hz, 4'-H), 7.15 (1H, d, 3.7Hz, 3'-H), and 7.57 (1H, m, 5'-H); m/z 612 (M $^+$, 1%), 597 (1), 117 (90), and 73 (100). (Found: M $^+$,

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612.2979. $C_{29}H_{52}O_8Si_3$ requires M , 612.2970). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

5 c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(furan-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 8b (0.6g, 0.98mmol) was deprotected to give the title compound (0.289g, 74%); ν_{max} (KBr) 10 3472, 1627, 1467, 1087, and 1046cm⁻¹; λ_{max} (EtOH) 321.5nm (ϵ_m 20,440); δ_H (CDCl₃) *inter alia* 0.93 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 6.17 (1H, s, 2-H), 6.55 (1H, dd, J 3.5 and 1.7Hz, 4'-H), 7.16 (1H, d, J 3.5Hz, 3'-H), and 7.58 (1H, s, with fine coupling, 5'-H); δ_C (CDCl₃/CD₃OD); 12.5 (C-17), 20.6 (C-14), 31.6 (C-9), 39.6 (C-8), 41.2 (C-4), 15 42.6 (C-12), 55.6 (C-10), 61.1 (C-11), 65.6 (C-16), 68.7 (C-6), 70.1 (C-7), 71.0 (C-13), 74.0 (C-5), 96.8 (C-2), 112.5 (C-4'), 116.0 (C-3'), 146.2 (C-5'), 150.1 (C-2'), 175.1 (C-3), and 191.1 (C-1); m/z 396 (M^+ , 1%) and 137 (100). (Found: M^+ , 396.1784. $C_{20}H_{28}O_8$ requires M , 396.1784). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

20 Example 9

25 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

30 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(pyrid-4-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

35 Using the method described in 5a, and on the same scale, pyridine-4-carboxaldehyde (0.32ml, 3.36mmol) was reacted to give the title compound (1.20g, 68%); δ_H (CDCl₃) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 5.14-5.22 (1H, m, 1-H), 7.34-7.38 (2H, m, 3' and 5'-H), and 8.56-8.60 (2H, m, 2' and 6'-H); m/z 625 (M^+ , 3%) and 117 (100). (Found: M^+ , 625.3288. $C_{30}H_{55}NO_7Si_3$ requires M , 625.3286).

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b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(pyrid-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

- 5 Using the method described in 6b, the product from 9a(1.18g, 1.88mmol) in benzene (60ml) was reacted with manganese dioxide (3.3g) for 2 hours to give the title compound (0.556g, 47%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 6.33 (1H, s, 2-H), 7.75-7.79 (2H, m, 3' and 5'-H), and 8.76 (2H, br, 2' and 6'-H); m/z 623 (M^+ , 4%), 117 (99), and 73 (100). (Found: M^+ , 623.3131. $C_{30}H_{53}NO_7Si_3$ requires M , 623.3130). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

- Using the method described in 5c, the product from 9b (0.535g, 0.86mmol) was deprotected to give the title compound (0.321g, 92%); ν_{max} (KBr) 20 3421, 1595, 1550, 1455, 1111, and 1062cm⁻¹; λ_{max} (EtOH) 316.5nm (ϵ_m 10,786); δ_H ($CDCl_3/CD_3OD$) *inter alia* 0.93 (3H, d, J 7.1Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 2.63 (1H, dd, J 15.1 and 8.5Hz, 4-H), 2.73 (1H, dd, J 7.6 and 2.1Hz, 11-H), 2.82 (1H, td, J 5.7 and 2.1Hz, 10-H), 2.98 (1H, dd, J 15.1 and 3.3Hz, 4-H), 6.33 (1H, s, 2-H), 7.69-7.73 (2H, m, 3' and 5'-H), and 8.70-8.75 (2H, m, 2' and 6'-H); δ_C ($CDCl_3/CD_3OD$); 12.5 (C-17), 20.6 (C-14), 31.6 (C-9), 39.8 (C-8), 42.6 (C-12), 43.2 (C-4), 55.6 (C-10), 61.0 (C-11), 65.6 (C-16), 68.5(C-6), 70.1 (C-7), 70.9 (C-13), 73.9 (C-5), 98.6 (C-2), 120.6 (C-3' and 5'), 141.9 (C-4'), 150.2 (C-2' and 6'), 177.1 (C-3), and 198.6 (C-1); m/z 407 (M^+ , 6%) and 148 (100). (Found: M^+ , 407.1954.
- 30 $C_{21}H_{29}NO_7$ requires M , 407.1944). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 10

35 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(pyrid-3-yl)-

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4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.34g,
5 2.58mmol) and pyridine-3-carboxaldehyde (0.29ml, 3.1mmol) were reacted
to give the title compound (1.154g, 71%); δ_H (CDCl₃) *inter alia* 0.90 (3H,
d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 5.19-5.27 (1H, m, 1-H),
7.33 (1H, dd, J 7.8 and 4.9Hz 5'-H), 7.77-7.82 (1H, m, 4'-H), 8.54 (1H, dd, J
4.7 and 1.1Hz, 6'-H), and 8.62 (1H, d, J 1.6Hz, 2'-H) (contains
10 approximately 4% pyridine-3-carboxaldehyde).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(pyrid-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

15 Using the method described in 6b, the product from 10a(1.10g, 1.76mmol)
in benzene (70ml) was reacted with manganese dioxide (4.0g) for 2 1/2
hours to give the title compound (0.513g, 47%); δ_H (CDCl₃) *inter alia* 0.90
(3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 6.29 (1H, s, 2-H),
20 7.43 (1H, dd, J 7.9 and 4.9Hz, 5'-H), 8.20 (1H, dt, J 7.9 and 1.7Hz, 4'-H),
8.73 (1H, m, 6'-H), and 9.09 (1H, s with fine coupling, 2'-H); m/z 623 (M^+ ,
75%), and 331 (100). (Found: M^+ , 623.3118. C₃₀H₅₃NO₇Si₃ requires M ,
623.3130). The ¹H n.m.r. spectrum indicated that the title compound was
essentially in the enolic form.

25 c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

30 Using the method described in 5c, the product from 10b (0.50g, 0.80mmol)
was deprotected to give the title compound (0.262g, 81%); ν_{max} (KBr)
3411, 1597, 1452, 1111, and 1043cm⁻¹; λ_{max} (EtOH) 312nm (ϵ_m 12,785);
 δ_H (CDCl₃) 0.93 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.4Hz, 14-H₃),
6.34 (1H, s, 2-H), 7.42 (1H, dd, J 8.0 and 4.9Hz, 5'-H), 8.18 (1H, dt, J 8.0
35 and 1.7Hz, 4'-H), 8.72 (1H, dd, J 4.9 and 1.4Hz, 6'-H), and 9.07 (1H, d, J
1.8Hz, 2'-H); δ_C (CDCl₃) 12.8 (C-17), 20.8 (C-14), 31.6 (C-9), 39.8 (C-8),
42.5 (C-4), 42.8 (C-12), 55.5 (C-10), 61.0 (C-11), 65.5 (C-16), 68.6 (C-6),
70.3 (C-7), 71.2 (C-13), 73.6 (C-5), 97.9 (C-2), 123.6 (C-5'), 130.4 (C-3'),

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134.7 (C-4'), 148.1 (C-6'), 152.4 (C-2'), 179.4 (C-3), and 196.4 (C-1); m/z 407 (M^+ , 17%)
and 106 (100). (Found: M^+ , 407.1946. $C_{21}H_{29}NO_7$ requires M , 407.1944).
The 1H n.m.r. spectrum indicated that the title compound was essentially
5 in the enolic form.

Example 11

10 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-2-yl)but-1-yl]but-
1-yl]5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-
tetrahydropyran

15 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(pyrid-2-yl)-
4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-
silyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, trist trimethylsilylmonone (1.04g,
2mmol) and pyridine-2-carboxaldehyde (0.23ml, 2.4mmol) were reacted to
give the title compound (0.804g, 64%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J
20 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 5.21-5.27 (1H, m, 1-H), 7.22
(1H, m, 5'-H), 7.51 (1H, d, J 7.8Hz, 3'-H), 7.73 (1H, t with further fine
coupling, J 7.7Hz, 4'-H), and 8.54 (1H, d, J 4.7Hz, 6'-H); m/z 625 (M^+ , 3%),
129 (100), 117 (100), and 73 (100). (Found: M^+ , 625.3281. $C_{30}H_{55}NO_7Si_3$
requires M , 625.3286).

25 b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(pyrid-
2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-
methylhexyl)tetrahydropyran

30 Using the method described in 6b, the product from 11a(0.790g,
1.26mmol) in benzene (35ml) was reacted with manganese dioxide (2.5g)
for 2 hours to give the title compound (0.275g, 35%); δ_H ($CDCl_3$) inter alia
0.89 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃),
6.89 (1H, s, 2-H), 7.37-7.44 (1H, m, 5'-H), 7.83 (1H; dt, J 1.7 and 7.8Hz,
35 4'-H), 8.08 (1H, d, J 7.8Hz, 3'-H), 8.67 (1H, d, J 4.2Hz, 6'-H); m/z 623 (M^+ ,
14%), 148 (75), 117 (82), and 73 (100). (Found: M^+ , 623.3143.
 $C_{30}H_{53}NO_7Si_3$ requires M , 623.3130). The 1H n.m.r. spectrum indicated
that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(pyrid-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

5

Using the method described in 5c, the product from 11b (0.260g, 0.42mmol) was deprotected to give the title compound (0.042g, 25%); ν_{max} (KBr) 3399, 1607, 1587, 1516, 1449, and 1045cm⁻¹; λ_{max} (EtOH) 314nm (ϵ_m 11,010); δ_H [(CD₃)₂CO] *inter alia* 0.92 (3H, d, J 7.0Hz, 17-H₃), 1.16 (3H, d, J 6.4Hz, 14-H₃), 6.98 (1H, s, 2-H), 7.57 (1H, ddd, J 7.4, 4.8, and 1.4Hz, 5'-H), 8.00 (1H, dt, J 7.7 and 1.7Hz, 4'-H), 8.10 (1H, d, J 7.8Hz, 3'-H), and 8.71 (1H, d, with further fine coupling, J 4.8Hz, 6'-H); *m/z* (TSP) 408 (MH^+ , 65%) and 99 (100); *m/z* 407 (M^+ , 40%) and 122 (100). (Found: M^+ , 407.1950. C₂₁H₂₉NO₇ requires M , 407.1944).

15

Example 12

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methylisoxazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

20

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3-methylisoxazol-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

25

Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and 3-methylisoxazole-5-carboxaldehyde (0.267g, 2.4mmol) were reacted to give the title compound (0.834g, 66%); δ_H (CDCl₃) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 2.29 (3H, s, 3'-CH₃), 5.18-5.27 (1H, m, 1-H), and 6.10 (1H, s, 4'-H); *m/z* 629 (M^+ , 8%), 129 (100), 117 (100), and 73 (100). (Found: M^+ , 629.3260. C₂₉H₅₅NO₈Si₃ requires M , 629.3236).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(3-methylisoxazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 12a(0.815g,

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1.29mmol) in benzene (35ml) was reacted with manganese dioxide (2.04g) for 2 hours to give the title compound (0.360g, 42%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 2.37 (3H, s, 3'-CH₃), 6.32 (1H, s, 2-H), and 6.69 (1H, s, 4'-H); m/z (TSP) 645 (MNH_4^+ , 100%) and 628 (MH^+ , 65); m/z 627 (M^+ , 10%), 612 (12), 117 (100), and 73 (100). (Found: M^+ , 627.3104. $C_{29}H_{53}NO_8Si_3$ requires M , 627.3079). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

- 10 c) $3R,4R$ -Dihydroxy-2S-[2,4-dioxo-4-(3-methylisoxazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 12b (0.380g, 0.6mmol) was deprotected to give the title compound (0.167g, 68%); ν_{max} (KBr) 3395, 1617, 1584, 1512, 1457, 1412, and 1055cm⁻¹; λ_{max} (EtOH) 330nm (ϵ_M 13,500); δ_H [$(CD_3)_2SO$] inter alia 0.83 (3H, d, J 7.1Hz, 17-H₃), 1.07 (3H, d, J 6.4Hz, 14-H₃), 2.25 (3H, s, 3'-CH₃), 5.83 (1H, s, 2-H), and 6.64 (1H, s, 4'-H); δ_C (CD_3OD) 11.3 (isox-CH₃), 12.3 (C-17), 20.4 (C-14), 32.9 (C-9), 41.5 (C-8), 43.7 (C-12), 45.1 (br, C-4), 56.9 (C-10), 61.3 (C-11), 66.5 (C-16), 70.1 (C-6), 70.8 (C-13), 71.6 (C-7), 76.0 (br, C-5), 99.0 (br, C-2), 106.6 (br, C-4'), 161.9 (C-3'), 170.5 (br, C-5'), 171.4 (br, C-3), and 197.0 (br, C-1); m/z (FAB, thioglycerol) 450 (MK^+) and 434 (MNa^+); m/z 411 (M^+ , 0.1%), 125 (80), and 43 (100). (Found: M^+ , 411.1892. $C_{20}H_{29}NO_8$ requires M , 411.1893). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 13

- 30 $3R,4R$ -Dihydroxy-2S-[2,4-dioxo-4-(3-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

- a) $3R,4R$ -Bistrimethylsilyloxy-2S-[4-(3-methoxyphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale,

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3-methoxybenzaldehyde (0.39ml, 3.2mmol) was reacted to give the title compound (1.06g, 56%);

δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 3.82 (3H, s, OMe), 4.07-4.20 (1H, m, 5-H), 5.09-5.21 (1H, m, 1-H),

5 6.78-6.85 (1H, m, 6'-H), 6.90-6.99 (2H, m, 2', 4'-H₂), 7.23-7.32 (1H, m, 5'-H); m/z 654 (M^+ , 0.5%) and 117 (100). (Found: M^+ , 654.3456.
 $C_{32}H_{58}O_8Si_3$ requires M , 654.3440).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(3-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 13a(1.0g, 1.49mmol) in benzene (50ml) was reacted with manganese dioxide (3.0g) for 3 hours 15 to give the title compound (0.610g, 61%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 3.86(3H, s, OMe), 6.25 (1H, s, 2-H), 7.06 (1H, dd, J 1.6, 8.0Hz, 6'-H), 7.35 (1H, dd, J 7.8, 8.0Hz, 5'-H), 7.40-7.51 (2H, m, 2', 4'-H₂); m/z 652 (M^+ , 1%) and 41 (100). (Found: M^+ , 652.3280. $C_{35}H_{56}O_8Si_3$ requires M , 652.3280).

20 c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

25 Using the method described in 5c, the product from 13b (250mg, 0.37mmol) was deprotected to give the title compound (140mg, 87%); ν_{max} (KBr) 3430, 1718, 1576, 1457cm⁻¹; λ_{max} (EtOH) 309nm (ϵ_m 15,360); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.4Hz, 14-H₃), 3.86 (3H, s, OMe), 6.26 (1H, s, 2-H), 7.08 (1H, d with further fine coupling, J ca.8.0Hz, 6'-H), 7.30-7.52 (3H, m, 2', 4', 5'-H₃); δ_C (d_4 -MeOH), 12.0 (C-17), 20.0 (C-14), 32.6 (C-9), 41.3 (C-8), 42.6 (C-4), 43.4 (C-12), 55.6 (C-10), 56.5 (OMe), 60.9 (C-11), 66.1 (C-16), 69.5 (C-6), 70.4 (C-13), 71.2 (C-7), 75.1 (C-5), 98.1 (C-2), 113.8 (C-5'), 119.0 (C-4'), 120.1 (C-6'), 130.5 (C-3), 137.1(C-1'), 161.0 (C-3'), 183.1 (C-3), 196.3 (C-1); m/z 436 (M^+ , 0.2%) and 135 (100). (Found: M^+ , 436.2105.
 $C_{27}H_{32}O_8$ requires M , 436.2097). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 14

5 3R,4R-Dihydroxy-2S-[4-(4-cyanophenyl)-2,4-dioxobut-1-
y1]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-
tetrahydropyran

10 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-cyanophenyl)-
4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-
silyloxy-4S-methylhexyl)tetrahydropyran

15 Using the method described in 5a, and on the same scale,
4-cyanobenzaldehyde (419mg, 3.2mmol) was reacted to give the title
compound (1.25g, 68%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz,
17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.08-4.19 (1H, m, 5-H), 5.16-5.28
15 (1H, m, 1-H), 7.49 (2H, d, J 8.2Hz, 2', 6'-H₂), 7.62 (2H, d, J 8.2Hz, 3',
5'-H₂).

20 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-cyanophenyl)-
2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyl-
oxy-4S-methylhexyl)tetrahydropyran

25 Using the method described in 6b, the product from 14a(1.25g) in benzene
(65ml) was reacted with manganese dioxide (3.5g) for 1 hour to give the
title compound (625mg, 50%); δ_H ($CDCl_3$) 0.90 (3H, d, J 7.0Hz, 17-H₃),
1.20 (3H, d, J 6.3Hz, 14-H₃), 1.31-1.45 (1H, m, 8-H), 1.50-1.66 (2H, m,
9-H), 1.80-1.90 (1H, m, 12-H), 2.39 (1H, dd, J 10.2, 14.8Hz, 4-H), 2.62-2.75
(2H, m, 10, 11-H₂), 2.86 (1H, dd, J 2.6, 14.7Hz, 4-H), 3.46 (1H, dd, J 2.4,
9.2Hz, 6-H), 3.57 (1H, d, J 11.3Hz, 16-H), 3.77-3.92 (2H, m, 7, 13-H₂), 3.96
(1H, d, J 11.3Hz, 16-H), 4.07-4.20 (1H, m, 5-H), 6.28 (1H, s, 2-H), 7.74
30 (2H, d, J 8.5Hz, 3', 5'-H₂), 7.97 (2H, d, J 8.5Hz, 2', 6'-H₂). The ¹H
spectrum indicated that the title compound was essentially in the enolic
form.

35 c) 3R,4R-Dihydroxy-2S-[4-(4-cyanophenyl)-2,4-dioxo-
but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-
tetrahydropyran

Using the method described in 5c, the product from 14b (200mg,

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0.31mmol) was deprotected to give the title compound (95mg, 71%); ν_{max} (KBr) 3431, 2230, 1597, 1558cm⁻¹; λ_{max} (EtOH) 321.5nm (ϵ_m 16,280); δ_{H} (CDCl₃) *inter alia* 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 6.29 (1H, s, 2-H), 7.75 (2H, d, J 8.4Hz, 3', 5'-H₂), 7.97 (2H, d, J 8.4Hz, 2', 6'-H₂); δ_{C} (CDCl₃) 13.1 (C-17), 21.2 (C-14), 31.9 (C-9), 40.1 (C-8), 43.2 (C-12), 43.3 (C-4), 56.0 (C-10), 61.6 (C-11), 66.0 (C-16), 69.2 (C-6), 70.6 (C-13), 71.7 (C-7), 74.2 (C-5), 98.8 (C-2), 115.8 (C-1'), 118.4 (C-4'), 127.8 (C-2', 6'), 132.8 (C-3', 5'), 138.7(CN), 179.1 (C-3), 198.1 (C-1); m/z (FAB) 454 (MNa^+). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 15

15 3R,4R-Dihydroxy-2S-[4-(4-chlorophenyl)-2,4-dioxo-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

20 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-chlorophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, 4-chlorobenzaldehyde (450mg, 3.2mmol) was reacted to give the title compound (1.4g, 76%); δ_{H} (CDCl₃) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.18 (3H, d, J 6.4Hz, 14-H₃), 4.07-4.18 (1H, m, 5-H), 5.08-5.20 (1H, m, 1-H), 7.28-7.32 (4H, m, Ar); m/z 658 (M^+ , 0.01%) and 117 (100). (Found: M^+ , 658.2947. C₃₁H₅₅O₇ClSi₃ requires M , 658.2944).

30 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-chlorophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 15a(700mg, 1.06mmol) in benzene (30ml) was reacted with manganese dioxide (1.75g) for 2 hours to give the title compound (296mg, 42%); δ_{H} (CDCl₃) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.10 (3H, d, J 6.3Hz, 14-H₃), 3.94-4.08 (1H, m, 5-H), 6.23 (1H, s, 2-H), 7.41 (2H, d, J 8.6Hz, 3', 5'-H₂), 7.82 (2H, d, J 8.6Hz, 2', 6'-H₂); m/z , 656 (M^+ , 5%) and 117 (100). (Found: M^+ , 656.2803.

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C₃₁H₅₃O₇ClSi₃ requires M, 656.2788).

- c) 3R,4R-Dihydroxy-2S-[4-(4-chlorophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

5 tetrahydropyran

Using the method described in 5c, the product from 15b (296mg, 0.45mmol) was deprotected to give the title compound (160mg, 80%); ν_{max} (KBr) 3424, 1718, 1595, 1486, 1451, 1380cm⁻¹; λ_{max} (EtOH) 313nm (ε_m 17,760) and 255 (7,460); δ_H (CDCl₃) *inter alia* 0.93 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 6.20 (1H, s, 2-H), 7.43 (2H, d, J 8.6Hz, 3', 5'-H₂), 7.82 (2H, d, J 8.6Hz, 2', 6'-H₂); δ_C (CDCl₃) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.7 (C-8), 42.7 (C-4), 42.8 (C-12), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 69.0 (C-6), 70.3 (C-13), 71.3 (C-7), 73.9 (C-5), 97.4 (C-2), 128.4 (C-3', C-5'), 129.0 (C-2', C-6'), 134.6 (C-1'), 140.4 (C-4'), 181.1 (C-3), 196.0 (C-1); m/z 441 (M⁺, 2%) and 139 (100). (Found: M⁺, 441.1680. C₂₂H₃₀O₇Cl requires M, 441.1680). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

20 Example 16

3R,4R-Dihydroxy-2S-[4-(4-diethoxymethylphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

25

- a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-diethoxy-methylphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

30

Using the method described in 5a, and on the same scale, terephthalaldehyde-mono, diethyl acetal (666mg, 3.2mmol) was reacted to give the title compound (1.52g, 75%); δ_H (d₄-MeOH) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.02-4.16 (1H, m, 5-H), 5.10-5.19 (1H, m, 1-H), 5.47 (1H, s, ArCH₂-(OEt)₂), 7.36 and 7.42 (4H, ABq, J 8.4Hz); m/z (FAB) 749 (MNa⁺).

35

- b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-diethoxy-methylphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-

trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 16a(1.0g, 1.38mmol) in benzene (50ml) was reacted with manganese dioxide (2.5g) for 2 hours
5 to give the title compound (535mg, 53%); δ_H (d_4 -MeOH) *inter alia* 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 1.22 (6H, t, J 7.1Hz,
-(OEt)₂), 4.07-4.17 (1H, m, 5-H), 5.55 (1H, s, Ar-CH-(OEt)₂), 6.41 (1H, s,
2-H), 7.56 (2H, d, J 8.3Hz, 3', 5'-H₂), 7.92 (2H, d, J 8.3Hz, 2', 6'-H₂); *m/z*
10 724 (*M*⁺, 0.1%) and 432 (100). (Found: *M*⁺, 724.3860. C₃₆H₆₄O₉Si₃
requires *M*, 724.3858). The ¹H n.m.r. spectrum indicated that the title
compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[4-(4-diethoxymethylphenyl)-
2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-
15 methylhexyl)tetrahydropyran

Using the method described in 1d, the product from 16b (150mg, 0.21mmol) in ethanol (5ml) was deprotected to give the title compound
20 (60mg, 57%); λ_{max} (EtOH) 315nm (ϵ_m 18,870) and 252 (7,350); δ_H (d_6 -acetone) *inter alia* 0.92 (3H, d, J 7.0Hz, 17-H₃), 1.10-1.30 (9H, m,
17-H₃, 2 x OEt), 5.58 (1H, s, -CH-(OEt)₂), 6.52 (1H, s, 2-H), 7.59 (2H, d, J
8.4Hz, 3', 5'-H₂), 7.99 (2H, d, J 8.4Hz, 2', 6'-H₂); δ_C (d_6 -acetone) 12.3
(C-17), 15.5 (-CH₂Me), 20.8 (C-14), 32.7 (C-9), 41.3 (C-8), 43.0 (C-4), 43.3
(C-12), 55.8 (C-10), 60.4 (C-11), 61.6 (-CH₂Me), 66.0 (C-16), 69.4 (C-6),
25 70.1 (C-7), 71.1 (C-13), 75.1 (C-5), 98.0 (C-2), 101.6 (CH-(OEt)₂), 127.6 and
127.7 (C-2', 6', 3', 5'), 135.5 (C-4'), 144.9 (C-1'), 183.0 (C-1), 197.2 (C-3).
The ¹H n.m.r. spectrum indicated that the title compound was essentially
in the enolic form.

30 Example 17

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-formylphenyl)-but-1-
yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-
tetrahydropyran

35 a) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-
formylphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-
sOxyloxy-4S-methylhexyl)tetrahydropyran

- The product from 16b (110mg) was dissolved in acidic chloroform (10ml) [standard solution: chloroform (100ml):concentrated hydrochloric acid (1 drop)]. After 1 1/2 hours the mixture was evaporated and
- 5 chromatographed on silica eluting with ethyl acetate/hexane mixtures to give the title compound (60mg, 60%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.2Hz, 14-H₃), 4.08-4.22 (1H, m, 5-H), 6.33 (1H, s, 2-H), 7.95 and 8.04 (4H, ABq, J 8.4Hz, Ar), 10.09 (1H, s, -CHO); m/z (FAB) 673 (MNa^+).
- 10 b) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-formylphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran
- 15 Using the method described in 5c, the product from 17a (50mg, 0.08mmol) was deprotected to give the title compound (33mg, 100%); ν_{max} (KBr) 3427, 1701, 1602, 1564cm⁻¹; λ_{max} (EtOH) 322.5nm (ϵ_m 16,240) and 258 (9,430); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 6.33 (1H, s, 2-H), 7.94 and 8.01 (4H, ABq, J 8.3Hz, Ar), 10.06 (1H, s, -CHO); δ_C ($CDCl_3$) 12.8 (C-17), 20.9 (C-14), 31.6 (C-9), 39.8 (C-8), 42.9 (C-12), 43.2 (C-4), 55.7 (C-10), 61.3 (C-11), 65.7 (C-16), 69.0 (C-6), 70.3 (C-7), 71.4 (C-13), 73.9 (C-5), 98.2 (C-2), 127.6 (C-3', 5'), 129.8 (C-2', 6'), 138.6 (C-4'), 139.5 (C-1'), 179.3 (C-1), 191.6 (CHO), 197.9 (C-3); m/z 434 (M^+ , 2%) and 133 (100); (Found: M^+ , 434.1944. $C_{23}H_{30}O_8$ requires M^+ , 434.1941). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 18

- 30 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran
- a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(4-nitrophenyl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran
- 35

Using the method described in 5a, and on the same scale, 4-nitrobenzaldehyde (483mg, 3.2mmol) was reacted to give the title

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compound (1.42g, 76%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 4.08-4.17 (1H, m, 5-H), 5.22-5.33 (1H, m, 1-H), 7.55 (2H, dd, J 1.5, 8.7Hz, 2', 6'-H₂), 8.21 (2H, d, J 8.7Hz, 3', 5'-H₂); m/z 669 (M^+ , 5%) and 117 (100). (Found: M^+ , 669.3198.

5 $C_{31}H_{55}NO_9Si_3$ requires M , 669.3185).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-nitrophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

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Using the method described in 6b, the product from 18a(1.0g, 1.49mmol) in benzene (50ml) was reacted with manganese dioxide (2.5g) for 45 minutes to give the title compound (618mg, 68%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.08-4.22 (1H, m, 5-H), 6.32 (1H, s, 2-H), 8.04 (2H, d, J 8.8Hz, 2', 6'-H₂), 8.30 (2H, d, J 8.8Hz, 3', 5'-H₂); m/z 667 (M^+ , 5%) and 117 (100). (Found: M^+ , 667.3043. $C_{31}H_{53}NO_9Si_3$ requires M , 667.3043). The 1H spectrum indicated that the title compound was essentially in the enolic form.

20

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

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Using the method described in 5c, the product from 18b (200mg, 0.3mmol) was deprotected to give the title compound (83mg, 61%); ν_{max} (KBr) 3112, 1588, 1488, 1451, 1346cm⁻¹; λ_{max} (EtOH) 331.5nm (ϵ_m 13,490) and 253.5 (9,430); δ_H ($CDCl_3$) *inter alia* 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.2Hz, 14-H₃), 6.32 (1H, s, 2-H), 8.03 (2H, d, J 8.9Hz, 2', 6'-H₂), 8.30 (2H, d, J 8.9Hz, 3', 5'-H₂); δ_C ($CDCl_3$) 12.8 (C-17), 20.9 (C-14), 31.6 (C-9), 39.8 (C-8), 42.9 (C-12), 43.1 (C-4), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 68.9 (C-7), 70.4 (C-6), 71.4 (C-13), 73.9 (C-5), 98.8 (C-2), 123.8 (C-2', 6'), 128.0 (C-3', 5'), 140.0 (C-1'), 149.9 (C-4'), 178.2 (C-1), 198.1 (C-3); m/z (FAB) 469 (MNH_4^+) and 452 (MH^+). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

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Example 19

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-2-yl)but-1-yl]-5S-

(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

- 5 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(thien-2-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.15g, 2.22mmol) and thiophene-2-carboxaldehyde (0.24ml, 2.6mmol) were reacted to give the title compound (1.086g, 78%); δ_H ($CDCl_3$) *inter alia* 10 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 5.36-5.46 (1H, m, 1-H), 6.94-7.00 (2H, m, 3' and 4'-H), and 7.22-7.28 (1H, m, 5'-H); *m/z* 630 (M^+ , 4%) and 117 (100). (Found: M^+ , 630.2909. $C_{29}H_{54}O_7SSi_3$ requires M , 630.2898).

- 15 b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(thien-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 19a (1.05g, 1.66mmol) in benzene (40ml) was reacted with manganese dioxide (2.6g) for 1 3/4h to give the title compound (0.684g, 66%); δ_H ($CDCl_3$) *inter alia* 20 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 6.13 (1H, s, 2-H), 7.12 (1H, dd, J 3.9 and 4.9Hz, 4'-H), 7.59 (1H, dd, J 0.9 and 4.9Hz, 3'-H), and 7.70 (1H, dd, J 0.9 and 3.9Hz, 5'-H); *m/z* 628 (M^+ , 2%), 336 (90), 117 (100), and 25 73 (99). (Found: M^+ , 628.2759. $C_{29}H_{52}O_7SSi_3$ requires M , 628.2742). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

- 30 c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 19b (0.670g, 1.06mmol) was deprotected to give the title compound (0.367g, 84%); ν_{max} (KBr) 3421, 1611, 1412, 1272, 1110, and 1043cm⁻¹; λ_{max} (EtOH) 325nm (ε_m 15,308); δ_H ($CDCl_3$) *inter alia* 35 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 6.13 (1H, s, 2-H), 7.14 (1H, dd, J 3.9 and 4.9Hz, 4'-H), 7.62 (1H, dd, J 4.9 and 0.9Hz, 3'-H), and 7.72 (1H, dd, J 3.9 and 0.9Hz, 5'-H); δ_C ($CDCl_3$) 12.7 (C-17), 20.7 (C-14), 31.6 (C-9), 39.6 (C-8), 40.8 (C-4),

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- 42.8 (C-12), 55.6 (C-10), 61.2 (C-11), 65.6 (C-16), 68.8 (C-6), 70.3 (C-7),
71.3 (C-13), 74.0 (C-5), 97.3 (C-2), 128.3, 130.6 and 132.6 (C-3', 4', 5'),
140.9 (C-2'), 180.7 (C-3), and 189.3 (C-1); m/z 412 (M^+ , 1%) and 111 (100).
5 The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic
form.

Example 20

10 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-3-yl)but-1-yl]-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

15 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(thien-
3-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-
4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.15g,
2.22mmol) and thiophene-3-carboxaldehyde (0.23ml, 2.6mmol) were
reacted to give the title compound (0.953g, 68%); δ_H ($CDCl_3$) *inter alia*
20 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 5.21-5.29 (1H,
m, 1-H), 7.04-7.09 (1H, m, 4'-H), 7.22-7.24 (1H, m, 2'-H), and 7.28-7.32
(1H, m, 5'-H); m/z 630 (M^+ , 0.1%), 226 (65), 129 (92), 117 (88), and 73
(100). (Found: M^+ , 630.2897. $C_{29}H_{54}O_7SSi_3$ requires M , 630.2898).

25 b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(thien-
3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-
methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 20a (0.93g, 1.47mmol)
30 in benzene (40ml) was reacted with manganese dioxide (2.5g) for 1 3/4h to
give the title compound (0.537g, 58%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J
7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 6.10 (1H, s, 2-H), 7.34 (1H,
dd, J 3.0 and 5.1Hz, 4'-H), 7.46 (1H, dd, J 1.1 and 5.1Hz, 5'-H), and 8.01
(1H, dd, J 1.1 and 3.0Hz, 2'-H); m/z 628 (M^+ , 2%), 336 (78), 117 (85), and
35 73 (100). (Found: M^+ , 628.2753. $C_{29}H_{52}O_7SSi_3$ requires M , 628.2742).
The 'H n.m.r. spectrum indicated that the title compound was essentially
in the enolic form.

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c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(thien-3-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

- 5 Using the method described in 6c, the product from 20b (0.53g, 0.84mmol) was deprotected to give the title compound (0.309g, 89%); ν_{max} (KBr) 3417, 1609, 1508, 1258, 1109, and 1054cm⁻¹; λ_{max} (EtOH) 313nm (ϵ_{m} 16,375); δ_{H} (CDCl₃) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.2Hz, 14-H₃), 7.36 (1H, dd, J 2.9 and 5.1Hz, 4'-H), 7.45 (1H, dd, J 1.2 and 5.1Hz, 5'-H), and 8.04 (1H, dd, J 1.2 and 2.9Hz, 2'-H); δ_{H} (CDCl₃) 12.6 (C-17), 20.7 (C-14), 31.6 (C-9), 39.6 (C-8), 42.3 (C-4), 42.7 (C-12), 55.6 (C-10), 61.2 (C-11), 65.6 (C-16), 68.9 (C-6), 70.2 (C-7), 71.2 (C-13), 73.8 (C-5), 98.0 (C-2), 125.8, 126.6 and 129.9 (C-2', 4' and 5'), 138.1 (C-3'), 177.9 (C-3), and 194.9 (C-1); m/z 412 (M⁺, 2%), 394 (7), 153 (70), and 111 (100).
10 (Found: M⁺, 412.1563. C₂₀H₂₈O₇S requires M, 412.1556). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.
15

Example 21

20

3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

- 25 a) 2-Dimethylaminopyridine-5-carboxaldehyde

5-Bromo-2-dimethylaminopyridine (1.005g, 5.0mmol) was dissolved in dry THF (25ml), cooled to -70°C, and treated dropwise with nbutyllithium (1.5M, 3.67ml, 5.5mmol). The mixture was stirred at -70°C for 1h, then 30 N,N-dimethyl-formamide (1.16ml, 15mmol) added. Stirring was continued for a further hour, then the reaction quenched with saturated ammonium chloride. Water was added, and the mixture extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried and evaporated. The crude product was purified by column chromatography, on silica (36g), eluting with 20, 40 and 60% ethyl acetate in hexane, to give the title compound as white crystals (0.617g, 82%); m.p. 55-55.5°C; δ_{H} (CDCl₃) 3.22 (6H, s, N(CH₃)₂), 6.56 (1H, d, J 9.0Hz, 3'-H), 7.92 (1H, dd, J 9.0 and 2.3Hz, 4'-H), 8.56 (1H, d, J 2.3Hz, 6'-H), and 9.77 (1H, s, CHO);
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m/z 150 (M⁺, 100%), 135 (83), 121 (88), and 44 (86). (Found: M⁺, 150.0795. C₈H₁₀N₂O requires M, 150.0793).

- 5 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-dimethylamino-pyrid-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-dimethylaminopyridine-5-carboxaldehyde (0.330g, 10 2.2mmol) were reacted to give the title compound (1.04g, 78%); δ_H (CDCl₃) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 3.09 (6H, s, N(CH₃)₂), 5.04-5.11 (1H, m, 1-H), 6.52 (1H, d, J 8.8Hz, 3'-H), 7.52 (1H, dt, J 8.8 and 2.8Hz, 4'-H), and 8.13 (1H, d, J 2.3Hz, 6'-H); m/z 668 (M⁺, 3%), 226 (100), 129 (90), 117 (80), and 73 (70). (Found: M⁺, 15 668.3724. C₂₂H₆₀N₂O₇Si₃ requires M, 668.3708).

- c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-dimethylamino-pyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 6b, the product from 21b (1.01g, 1.51mmol) in benzene (35ml) was reacted with manganese dioxide (2.6g) for 3h to give the title compound (0.440g, 44%); δ_H (CDCl₃) inter alia 0.89 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 3.18 (6H, s, N(CH₃)₂), 6.13 (1H, s, 2-H), 6.51 (1H, d, J 9.1Hz, 3'-H), 7.96 (1H, dd, J 9.1 and 2.4Hz, 4'-H), and 8.72 (1H, d, J 2.4Hz, 6'-H); m/z 666 (M⁺, 11%), 651 (3), and 149 (100). (Found: M⁺, 666.3551. C₃₂H₅₈N₂O₇Si₃ requires M, 666.3552). The 'H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

- 30 d) 3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

35 Using the method described in 5c, the product from 21c (0.420g, 0.63mmol) was deprotected to give the title compound (0.238g, 84%); ν_{max} (KBr) 3371, 1624, 1554, 1401, 1105, 1059, and 785cm⁻¹; λ_{max} (EtOH) 355nm (ε_m 35,913); δ_H (CDCl₃/CD₃OD) inter alia 0.93 (3H, d, J 7.0Hz,

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17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 3.19 (6H, s, N(CH₃)₂), 6.13 (1H, s, 2-H), 6.53 (1H, d, J 9.1Hz, 3'-H), 7.94 (1H, dd, J 2.3 and 9.1Hz, 4'-H), and 8.71 (1H, d, J 2.3Hz, 6'-H); δ _C (CDCl₃/CD₃OD) 12.6 (C-17), 20.6 (C-14), 31.7 (C-9), 38.1 (N(CH₃)₂), 39.6 (C-8), 41.8 (C-4), 42.7 (C-12), 55.7 (C-10), 5 61.2 (C-11), 65.6 (C-16), 68.9 (C-6), 70.2 (C-7), 71.1 (C-13), 74.0 (C-5), 95.6 (C-2), 105.1 (C-4'), 118.0 (C-5'), 135.9 (C-3'), 149.1 (C-6'), 160.6 (C-2'), 183.3 (C-3), and 191.5 (C-1); m/z 450 (M^+ , 5%) and 149 (100). (Found: M^+ , 450.2372. C₂₃H₃₄N₂O₇ requires M , 450.2366). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

10

Example 22

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

15

a) 2-Methylthiopyridine-5-carboxaldehyde

Using the method described in 21a, 5-bromo-2-methylthio-pyridine (1.020g, 5mmol) was converted to the title compound (0.650g, 85%); 20 m.p.43-45°C; δ _H (CDCl₃) 2.64 (3H, s, SCH₃), 7.31 (1H, d, J 8.5Hz, 3'-H), 7.94 (1H, dd, J 2.1 and 8.5Hz, 4'-H), 8.84 (1H, d, J 2.1Hz, 6'-H), and 10.00 (1H, s, CHO); m/z 153 (M^+ , 100%), 152 (60), 124 (10), and 107 (48). (Found: M^+ , 153.0247. C₇H₇NOS requires M , 153.0248).

25

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-methylthiopyrid-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (2.750g, 30 5.3mmol) and 2-methylthiopyridine-5-carboxaldehyde (0.890g, 5.8mmol) were reacted to give the title compound (2.840g, 80%); δ _H (CDCl₃) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 2.59 (3H, s, SCH₃), 5.11-5.19 (1H, m, 1-H), 7.20 (1H, d, J 8.3Hz, 3'-H), 7.58 (1H, dt, J 8.3 and 2.8Hz, 4'-H), and 8.43 (1H, d, J 2.0Hz, 6'-H); m/z 671 (M^+ , 2%), 35 129 (65), 117 (85), and 73 (100). (Found: M^+ , 671.3187. C₃₁H₅₇NO₇SSi₃ requires M , 671.3164).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-

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methylthiopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 22b (2.09g, 3.11mmol)
5 in benzene (150ml) was reacted with manganese dioxide (2.8g) for 24h to give the title compound (1.340g, 64%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 2.61 (3H, s, SCH₃), 6.23 (1H, s, 2-H), 7.24 (1H, d, J 8.5Hz, 3'-H), 7.95 (1H, dd, J 2.2 and 8.5Hz, 4'-H),
10 and 8.91 (1H, d, J 2.2Hz, 6'-H); m/z 669 (M^+ , 3%), 152 (45), 117 (95), 75 (56), and 73 (100). (Found: M^+ , 669.3018. $C_{31}H_{55}NO_7SSi_3$ requires M , 669.3007). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 22c (0.648g, 0.97mmol) was deprotected to give the title compound (0.341g, 78%);
20 m.p. 135.5-136°C; found C, 57.91; H, 6.88; N, 3.09; S, 7.10%. $C_{22}H_{31}NO_7S$ requires C, 58.26; H, 6.89; N, 3.09; S, 7.07%; ν_{max} (KBr) 3483, 3392, 1583, 1298, 1120, 1106, and 1061cm⁻¹; λ_{max} (EtOH) 336nm (ϵ_m 29,695); δ_H ($CDCl_3/CD_3OD$) *inter alia* 0.93 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.4Hz, 14-H₃), 2.61 (3H, s, SCH₃), 6.26 (1H, s, 2-H), 7.27 (1H, d, J 8.5Hz, 3'-H), 7.98 (1H, dd, J 8.5 and 2.3Hz, 4'-H), and 8.89 (1H, d, J 2.3Hz, 6'-H);
25 δ_C ($CDCl_3/CD_3OD$) 12.3 (C-17), 13.2 (SCH₃), 20.3 (C-14), 31.6 (C-9), 39.7 (C-8), 42.0 (C-4), 42.5 (C-12), 55.6 (C-10), 60.9 (C-11), 65.6 (C-16), 68.4 (C-6), 70.0 (C-7), 70.6 (C-13), 73.9 (C-5), 97.0 (C-2), 120.8 (C-4'), 125.9 (C-5'), 133.9 (C-3'), 148.1 (C-6'), 165.2 (C-2'), 180.5 (C-3), and 194.6 (C-1); m/z 453 (M^+ , 1%), 167 (100) and 152 (65). (Found: M^+ , 453.1825. $C_{22}H_{31}NO_7S$ requires M , 453.1821). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 23

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3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylsulphinylpyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

The product from 22c (0.215g, 0.32mmol) was dissolved in dichloromethane (9ml), cooled in an ice bath, saturated sodium hydrogen carbonate (0.5ml) and water (1.5ml) were then added, followed by 3-
5 chloroperbenzoic acid (ca.95%, 0.064g, 0.35mmol). The mixture was stirred for 3/4h, then separated, and the aqueous extracted with dichloromethane (x2). The combined organic phases were washed with brine, dried and evaporated. The product was purified by column chromatography, on silica (10g), eluting with 30-40% ethyl acetate in
10 hexane, to give the pure product (0.152g, 69%).

This material was dissolved in THF (7ml), water (0.7ml) added, followed by glacial acetic acid (0.7ml). Further portions of glacial acetic acid (5 x 0.4ml) were added over the following 28h. After this the solution was
15 evaporated to dryness, and purified by column chromatography to give the title compound (0.064g, 62%); ν_{max} (KBr) 3405, 1602, 1451, 1109, 1084, and 1042cm⁻¹; λ_{max} (EtOH) 322nm (ϵ_m 15,550); δ_{H} (CDCl₃) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.23 (3H, d, J 6.3Hz, 14-H₃), 2.90 (3H, s, SOCH₃), 6.33 and 6.35 (1H, 2s, 2-H), 8.13 (1H, d, J 8.2Hz, 3'-H), 8.39 (1H, 20 br d, 4'-H), and 9.06 (1H, s, 6'-H); δ_{C} (CDCl₃) 12.8 (C-17), 20.9 (C-14), 31.7 (C-9), 39.9 (C-8), 41.1, 42.7 and 42.8 (C-4, C-12 and SOCH₃), 55.6 (C-10), 61.1 (C-11), 65.6 (C-16), 68.8 (C-6), 70.4 (C-7), 71.3 (C-13), 73.9 (C-5), 98.5 (C-2), 119.4 (C-4'), 131.5 (C-5'), 136.5 (C-3'), 148.3 (C-6'), 169.0 (C-2'), 178.3 (C-3), and 197.2 (C-1); m/z (FAB, thioglycerol) 491 (MNa⁺) and 470 (MH⁺). The spectra indicated that the compound was a mixture of sulphoxide isomers, and essentially in the enolic form.

Example 24

30 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylsulphonylpyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

The product from 22c (0.235g, 0.35mmol) was dissolved in dichloromethane (15ml), saturated sodium hydrogen carbonate (1.5ml) and water (3ml) added, and the mixture stirred while 3-chloroperbenzoic acid (ca.95%, 0.140g, 0.77mmol) was added. Stirring was continued for seven hours, then water added and the mixture extracted with

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dichloromethane (x3). The combined organic extracts were dried and evaporated. The crude material was purified by column chromatography, on silica (10g), eluting with 25-40% ethyl acetate in hexane, to give the pure product (0.097g, 40%).

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This material was deprotected using the method described in 5c, to give the title compound (0.037g, 57%); ν_{max} (KBr) 3490, 1623, 1307, 1163, 1103, 1060, and 778cm⁻¹; λ_{max} (EtOH) 320nm (ϵ_m 14,012); δ_H (CDCl₃/CD₃OD) *inter alia* 0.94 (3H, d, J 7.1Hz, 17-H₃), 1.22 (3H, d, J 6.4Hz, 14-H₃), 3.29 (3H, S, SO₂CH₃), 6.38 (1H, S, 2-H), 8.18 (1H, d, J 8.2Hz, 3'-H), 8.45 (1H, dd, J 8.2 and 2.0Hz, 4'-H), and 9.16 (1H, d, J 2.0Hz, 6'-H); m/z 485 (M^+ , 0.1%), 135 (70), and 122 (100); m/z (FAB, thioglycerol) 498 (MNa^+) and 486 (MH^+). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

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Example 25

3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

20

a) N-Methoxy N-methyl-2-chloropyridine-5-carboxamide

2-Chloropyridine-5-carboxylic acid (1.576g, 10mmol) was dissolved in dry THF (100ml), cooled in an ice-bath, then triethylamine (1.5ml, 11mmol) added, followed by iso-butylchloroformate (1.3ml, 10mmol). The mixture was stirred for 3/4h, then N,O-dimethylhydroxylamine (*ex* hydrochloride salt, 15mmol) in dichloromethane (70ml) was added. After stirring for 1 3/4h, the mixture was diluted with dichloromethane, washed with water, aqueous sodium hydrogen carbonate, and brine, dried and evaporated. The crude product was purified by column chromatography, on silica (25g), eluting with 40% ethyl acetate in hexane, to give the title compound (1.280g, 64%); δ_H (CDCl₃) 3.35 and 3.55 (6H, 2s, 2 x CH₃), 7.35 (1H, d, J 8Hz, 3'-H), 8.0 (1H, dd, J 8 and 2Hz, 4'-H), and 8.7 (1H, d, J 2Hz, 6'-H).

35

b) 2-Chloropyridine-5-carboxaldehyde

The product from 25a (1.25g, 6.23mmol) was dissolved in dry

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- dichloromethane (25ml), cooled to -70°C, and treated dropwise with diisobutylaluminium hydride (1.0M in toluene, 9.3ml, 9.3mmol). After stirring for 1h at -70°C, the reaction was quenched with methanol and saturated sodium sulphate solution. The mixture was filtered, the phases separated, the organic washed with brine, dried and evaporated. The crude product was purified by column chromatography, on silica (18g), eluting with 20% ethyl acetate in hexane, to give the title compound (0.743g, 84%); m.p.80-81°C; found C, 50.86; H, 2.60; N, 9.85; Cl, 24.83%. C_6H_4ClNO requires C, 50.91; H, 2.85; N, 9.89; Cl, 25.05%; ν_{max} (CH_2Cl_2) 1713, 1584, 1560, 1349, 1102, and 837cm^{-1} ; δ_H ($CDCl_3$) 7.52 (1H, d, J 8.3Hz, 3'-H), 8.15 (1H, dd, J 2.3 and 8.3Hz, 4'-H), 8.87 (1H, d, J 2.3Hz, 6'-H), and 10.11 (1H, s, CHO); m/z 141/143 (M^+ , 75 and 25%), 140/142 (100 and 37), and 112/114 (54 and 18). (Found: M^+ , 140.9981. C_6H_4ClNO requires M , 140.9981).
- c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-chloropyrid-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl)tetrahydropyran
- Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-chloropyridine-5-carboxaldehyde (0.311g, 2.2mmol) were reacted to give the title compound (0.910g, 69%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 5.16-5.24 (1H, m, 1-H), 7.32 (1H, d, J 8.3Hz, 3'-H), 7.71 (1H, dt, J 8.3 and 2.3Hz, 4'-H), and 8.37 (1H, d, J 2.3Hz, 6'-H); m/z 660 (MH^+ , 3%), 129 (45), 117 (77), and 73 (100); m/z (FAB, 3-NOBA/Na) 682 (MNa^+) and 660 (MH^+). (Found: MH^+ , 660.2967. $C_{30}H_{55}ClNO_7Si_3$ requires M , 660.2978).
- d) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl)tetrahydropyran
- Using the method described in 6b, the product from 25c (0.880g, 1.33mmol) in benzene (40ml) was reacted with manganese dioxide (1.5g) for 3h, to give the title compound (0.442g, 50%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 6.24 (1H, s, 2-H), 7.42 (1H, d, J 8.4Hz, 3'-H), 8.13 (1H, d, J 8.4 and 2.4Hz, 4'-H), and 8.85 (1H, d, J 2.4Hz, 6'-H); m/z 657 (M^+ , 0.3%), 117 (70), and 73 (100).

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(Found: M^+ , 657.2747. $C_{30}H_{52}ClNO_7Si_3$ requires M , 657.2740). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

- 5 e) 3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

Using the method described in 5c, the product from 25d (0.420g, 10 0.64mmol) was deprotected to give the title compound (0.223g, 79%); ν_{max} (KBr) 3443, 1589, 1452, 1303, 1110, 1057, and 1015 cm^{-1} ; λ_{max} (EtOH) 316nm (ϵ_m 15,694); δ_H (CDCl₃/CD₃OD) *inter alia* 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.4Hz, 14-H₃), 6.33 (s, 2-H, partly exchanged), 7.50 (1H, d, J 8.4Hz, 3'-H), 8.20 (1H, dd, J 8.4 and 2.4Hz, 4'-H), and 8.86 (1H, d, J 2.4Hz, 6'-H); δ_C (CDCl₃/CD₃OD) 11.3 (C-17), 19.2 (C-14), 31.0 (C-9), 39.4 (C-8), 41.5 (C-4), 41.8 (C-12), 55.0 (C-10), 59.9 (C-11), 64.8 (C-16), 67.7 (C-6), 69.4 (C-13), 73.3 (C-7), 76.9 (C-5), 97.2 (C-2), 123.9 (C-3'), 129.1 (C-5'), 136.8 (C-4'), 147.7 (C-6'), 153.8 (C-2'), 177.8 (C-3), and 195.2 (C-1); m/z 441 (M^+ , 3%), 140/142 (100/35), and 69 (94). (Found: M^+ , 441.1559. 20 $C_{21}H_{28}ClNO_7$ requires M , 441.1554). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 26

- 25 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-hydroxymethylfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

a) 5-Triethylsilyloxymethylfuran-2-carboxaldehyde
30 5-Hydroxymethylfuran-2-carboxaldehyde (0.631g, 5mmol) was dissolved in dry dichloromethane (10ml), cooled in an ice-bath, and triethylamine (1.0ml, 7mmol) added followed by triethylchlorosilane (1.0ml, 6mmol). After stirring for 3/4h, the mixture was evaporated. The residue was purified by column chromatography, on silica (17g), eluting with 10% ethyl acetate in hexane, to give the title compound (1.194g, 99%); δ_H (CDCl₃) 0.55-0.8 (6H, m, 3 x CH₂), 0.85-1.15 (9H, m, 3 x CH₃), 4.65 (2H, s, CH₂O), 6.4 and 7.1 (2H, 2d, J 4Hz, 3 and 4-H), and 9.5 (1H, s, CHO).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(5-triethylsilyloxymethylfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

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Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 5-triethylsilyloxymethylfuran-2-carboxaldehyde (0.529g, 2.2mmol) were reacted to give the title compound (1.000g, 66%); δ_H ($CDCl_3$) inter alia 0.62 (6H, br q, 3 x CH_2), 0.86-1.0 (12H, m, 17- H_3 and 3 x CH_3), 1.20 (3H, d, J 6.8Hz, 14- H_3), 4.61 (2H, s, OCH_2), 5.13-5.20 (1H, m, 1-H), 6.19 and 6.21 (2H, 2d, J 3.2Hz, 3' and 4'-H); m/z (FAB, 3-NOBA/Na) 781 (MNa^+).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(5-triethylsilyloxymethylfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 26b (0.975g, 1.28mmol) in benzene (70ml) was reacted with manganese dioxide (4.1g) 20. for 3 1/2h to give the title compound (0.395g, 41%); δ_H ($CDCl_3$) inter alia 0.65 (6H, br q, 3 x CH_2), 0.86-1.01 (12H, m, 17- H_3 and 3 x CH_3), 1.20 (3H, d, J 6.4Hz, 14- H_3), 4.70 (2H, s, OCH_2), 6.14 (1H, s, 2-H), 6.41 (1H, d, J 3.5Hz, 4'-H), and 7.10 (1H, d, J 3.5Hz, 3'-H); m/z 756 (M^+ , 2%), 117 (100), and 73 (98). (Found: M^+ , 756.3949. $C_{36}H_{68}O_9Si_4$ requires M , 756.3940). 25 The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-hydroxymethylfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 26c (0.386g, 0.5mmol) was completely deprotected to give the title compound (0.153g, 72%); ν_{max} (KBr) 3411, 1618, 1209, 1101, and 1020 cm^{-1} ; λ_{max} (EtOH) 330nm (ε_m 19,562); δ_H ($CDCl_3/CD_3OD$) inter alia 0.94 (3H, d, J 7.0Hz, 17- H_3), 1.22 (3H, d, J 6.4Hz, 14- H_3), 4.62 (2H, s, OCH_2), 6.18 (s, 2-H, partly exchanged), 6.47 (1H, d, J 3.5Hz, 4'-H), and 7.16 (1H, d, J 3.5Hz, 3'-H); δ_C ($CDCl_3/CD_3OD$) 12.3 (C-17), 20.4 (C-14), 31.5 (C-9), 39.6 (C-8), 40.7 (C-4),

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42.5 (C-12), 55.6 (C-10), 56.9 (OCH₂), 60.9 (C-11), 65.4 (C-16), 68.4 (C-6),
70.1 (C-7), 70.7 (C-13), 73.9 (C-5), 96.7 (C-2), 110.0 (C-4'), 117.1 (C-3'),
149.4 (C-2'), 158.9 (C-5'), 175.4 (C-3), and 190.0 (C-1); m/z 426 (M^+ , 1%),
140 (100), 125 (92), and 69 (90). (Found: M^+ , 426.1900. C₂₁H₃₀O₉
5 requires M , 426.1890). The ¹H n.m.r. spectrum indicated that the title
compound was essentially in the enolic form.

Example 27

10 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-nitrothien-4-yl)but-1-
yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-
hydropyran

15 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-nitro-
thien-4-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-
silyloxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 5a, tristrimethylsilylmonone (1.038g,
2mmol) and 2-nitrothiophene-4-carboxaldehyde (0.346g, 2.2mmol) were
reacted to give the title compound (0.390g, 69%); δ_H (CDCl₃) *inter alia*
0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 5.11-5.21 (1H,
m, 1-H), 7.46-7.50 and 7.87-7.91 (2H, m, 3' and 5'-H); m/z (FAB, 3-
NOBA/Na) 698 (MNa^+).

25 b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-
nitrothien-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-tri-methyl-
silyloxy-4S-methylhexyl)tetrahydropyran

30 Using the method described in 6b, the product from 27a (0.500g,
0.74mmol) in benzene (35ml) was reacted with manganese dioxide (1.0g)
for 4 1/2h to give the title compound (0.186g, 37%); δ_H (CDCl₃) *inter alia*
0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 6.08 (1H, s,
2-H), 8.14 and 8.23 (2H, 2d, J 1.7Hz, 3' and 5'-H); m/z (FAB, thioglycerol)
674 (MH^+); m/z (FAB, 3-NOBA/Na) 718 (M + 2Na-H⁺). The ¹H n.m.r.
35 spectrum indicated that the title compound was essentially in the enolic
form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-nitrothien-4-yl)

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but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)
tetrahydropyran

- Using the method described in 5c, the product from 27b (0.170g,
 5 0.25mmol) was deprotected to give the title compound (0.095g, 83%); ν_{\max} (KBr) 3423, 1604, 1534, 1506, 1336, 1111, and 1052cm⁻¹; λ_{\max} (EtOH)
 10 311nm (ϵ_m 20,545); δ_H (CDCl₃) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃),
 1.22 (3H, d, J 6.3Hz, 14-H₃), 6.09 (1H, s, 2-H), 8.16 and 8.22 (2H, 2d, J
 15 1.7Hz, 3' and 5'-H); δ_C (CDCl₃/CD₃OD) 12.4 (C-17), 20.4 (C-14), 31.9 (C-
 9), 40.1 (C-8), 42.1 (C-4), 42.7 (C-12), 55.9 (C-10), 61.0 (C-11), 65.8 (C-16),
 68.6 (C-6), 70.2 (C-7), 70.6 (C-13), 74.2 (C-5), 98.1 (C-2), 126.7 and 134.5
 (C-3' and 5'), 137.8 (C-4'), 152.7 (C-2'), 175.8 (C-3), and 195.1 (C-1); m/z
 (FAB, thioglycerol) 475 (MNH₄⁺) and 458 (MH⁺); m/z (FAB, 3-NOBA/Na)
 502 (M + 2Na-H⁺) and 480 (MNa⁺).

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Example 28

- 3R,4R-Dihydroxy-2S-[4-(2-bromopyrid-5-yl)-2,4-dioxobut-1-
yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-
 20 hydropyran

a) N-Methoxy, N-methyl-2-bromopyridine-5-carboxamide

- Using the method described in 25a, 2-bromopyridine-5-carboxylic acid
 25 (2.02g, 10mmol) was reacted to give the title compound (1.637g, 67%); δ_H
 (CDCl₃) 3.35 and 3.55 (6H, 2s, 2 x CH₃), 7.55 (1H, d, J 8Hz, 3'-H), 7.9
 (1H, dd, J 8 and 2Hz, 4'-H), and 8.7 (1H, d, J 2Hz, 6'-H).

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- b) 2-Bromopyridine-5-carboxaldehyde
- Using the method described in 25b, N-methoxy, N-methyl-2-
 bromopyridine-5-carboxamide (1.60g, 6.53mmol) was reacted to give the
 title compound (1.042g, 86%); m.p.103.5-104°C (chloroform/hexane); found
 C, 38.72; H, 2.09; N, 7.53; Br, 42.62%. C₆H₄BrNO requires C, 38.74; H,
 35 2.17; N, 7.53; Br, 42.96%; δ_H [(CD₃)₂CO] 7.8 (1H, d, J 8Hz, 3'-H), 8.15
 (1H, dd, J 8 and 2Hz, 4'-H), 8.85 (1H, d, J 2Hz, 6'-H), and 10.15 (1H, s,
 CHO).

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c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-bromopyrid-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

5 Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-bromopyridine-5-carboxaldehyde (0.409g, 2.2mmol) were reacted to give the title compound (0.729g, 52%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 5.13-5.22 (1H, m, 1-H), 7.47 (1H, d, J 8.2Hz, 3'-H), 7.58-7.64 (1H, m, 4'-H), and 8.35 (1H, d, J 2.3Hz, 6'-H); m/z (NH_3 , DCI) 706/704 (MH^+ , 10%), 186/188 (50), 108 (50), and 90 (100).

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15 d) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-bromopyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 28c (0.721g, 1.02mmol) in benzene (40ml) was reacted with manganese dioxide (1.44g) for 2½ hours to give the title compound (0.320g, 45%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 6.24 (1H, s, 2-H), 7.59 (1H, d, J 8.3Hz, 3'-H), 8.01 (1H, dd, J 8.3 and 2.5Hz, 4'-H), and 8.82 (1H, d, J 2.5Hz, 6'-H); m/z 701/703 (M^+ , 1%), 409/411 (5), 117 (100), and 73 (97). (Found: M^+ , 701.2232. $C_{30}H_{52}BrNO_7Si_3$ requires M , 701.2235). The ¹H n.m.r. spectrum indicated that the compound was essentially in the enolic form.

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25 e) 3R,4R-Dihydroxy-2S-[4-(2-bromopyrid-5-yl)-2,4-dioxo-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

30 Using the method described in 5c, the product from 28d (0.310g, 0.44mmol) was deprotected to give the title compound (0.090g, 42%); m.p.133-134°C; found C, 51.53; H, 5.85; N, 2.94%; $C_{21}H_{28}BrNO_7$ requires C, 51.86; H, 5.80; N, 2.88%; ν_{max} (KBr) 3435, 1576, 1452, 1096, 1057, and 1013cm⁻¹; λ_{max} (EtOH) 313 (ϵ_m 18,198) and 248nm (8,079); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 6.47 (1H, s, 2-H), 7.73 (1H, d, J 8.5Hz, 3'-H), 8.16 (1H, dd, J 8.5 and 2.4Hz, 4'-H), and 8.86 (1H, d, J 2.4Hz, 6'-H); δ_C (CD_3OD) 12.3 (C-17),

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20.3 (C-14), 33.0 (C-9), 41.8 (C-8), 43.2 (C-4), 43.7 (C-12), 56.9 (C-10), 61.2 (C-11), 66.4 (C-16), 69.8 (C-6), 70.7 (C-13), 71.5 (C-7), 75.4 (C-5), 99.1 (C-2), 129.6 (C-3'), 131.5 (C-5'), 138.4 (C-4'), 146.4 (C-2'), 149.8 (C-6'), 179.7 (C-1), and 197.8 (C-3); m/z (NH₃ DCI) 486/488 (MH^+ , 30%), 200/202 (35), and 122 (100); m/z 485/487 (M^+ , 2%), 226/228 (48), 200/202 (70), 184/186 (80), 71 (85), and 69 (100). (Found: M^+ , 485.1022. C₂₁H₂₈BrNO₇ requires M , 485.1049). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

10 Example 29

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-methoxyfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

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a) 5-Methoxyfuran-2-carboxaldehyde

n-Butyllithium (1.5M, 7.3ml, 11mmol) was added slowly to diisopropylamine (1.5ml, 10.5mmol) in THF (20ml) at -30°C. Stirred for 20 10 mins, cooled to -70°C, and 2-methoxyfuran (0.981g, 10mmol) in THF (8ml) added slowly. After stirring for ½h dimethylformamide (2.4ml, 30mmol) was added, and the mixture stirred for a further 1h. After quenching with saturated aqueous ammonium chloride, the mixture was extracted with dichloromethane (x2). The combined organic extracts were 25 washed with brine, dried and carefully evaporated. The residue was purified twice by flash chromatography, eluting with ether/hexane mixtures, to give the title compound (0.463g, 37%); δ_H (CDCl₃) 4.05 (3H, s, OCH₃), 5.55 (1H, d, J 4Hz, 4-H), 7.3 (1H, d, J 4Hz, 3-H), and 9.35 (1H, s, CHO).

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b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(5-methoxyfuran-2-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

35 Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 5-methoxyfuran-2-carboxaldehyde (0.29g, 2.2mmol) were reacted to give the title compound (1.058g, 82%); δ_H (CDCl₃) inter alia 0.9 (3H, d, J 7Hz, 17-H₃), 1.2 (3H, d, J 6Hz, 14-H₃), 3.8 (OCH₃), 4.9-5.15 (2H,

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m, 1-H and 4'-H), and 6.1 (1H, d, δ 4Hz, 3'-H). The product was unstable, and readily dehydrated.

- 5 c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(methoxyfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 29b (1.01g, 1.57mmol) in benzene (40ml) was reacted with manganese dioxide (3.0g) for 4 hours 10 to give the title compound (0.159g, 16%); δ_H (CDCl₃) *inter alia* 0.90 (3H, d, δ 7.1Hz, 17-H₃), 1.20 (3H, d, δ 6.3Hz, 14-H₃), 3.96 and 3.97 (OCH₃), 5.39 (0.8H, d, δ 3.6Hz) and 5.41 (0.2H, d, δ 3.8Hz, 4'-H), 5.98 (0.8H, s, 2-H), and 7.14 (0.8H, d, δ 3.6Hz) and 7.23 (0.2H, d, δ 3.8Hz, 3'-H); *m/z* (NH₃ DCI) 643 (MH^+ , 22%) and 90 (100); *m/z* 643 (MH^+ , 3%), 125 (50), 15 117 (100), and 73 (72). (Found: MH^+ , 643.3140. C₃₀H₅₅O₉Si₃ requires MH^+ , 643.3154).

- 20 d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(5-methoxyfuran-2-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 29c (0.146g, 0.23mmol) was deprotected to give the title compound (0.080g, 82%); ν_{max} (KBr) 3432, 1718, 1627, 1523, 1426, and 1042cm⁻¹; λ_{max} (EtOH) 347nm 25 (ϵ_m 16,692); δ_H (CD₃OD) *inter alia* 0.94 (3H, d, δ 7.1Hz, 17-H₃), 1.20 (3H, d, δ 6.4Hz, 14-H₃), 3.97 (OCH₃), 5.59 (1H, d, δ 3.7Hz, 4'-H), 6.01 (1H, s, 2-H), and 7.29 (1H, d, δ 3.7Hz, 3'-H); δ_C (CD₃OD) 12.3 (C-17), 20.4 (C-14), 33.0 (C-9), 40.6 (C-4), 41.7 (C-8), 43.8 (C-12), 56.9 (C-10), 58.9 (OCH₃), 61.3 (C-11), 66.5 (C-16), 69.7 (C-6), 70.8 (C-13), 71.5 (C-7), 74.4 and 75.5 30 (C-5), 85.6 (C-4'), 96.7 (C-2), 122.3 (C-3'), 142.2 (C-2'), 166.4 (C-5'), 178.2 (C-1), and 187.0 (C-3); *m/z* (NH₃ DCI) 427 (MH^+ , 100%); *m/z* 426 (M^+ , 3%), 140 (60), and 125 (100). (Found: M^+ , 426.1892. C₂₁H₃₀O₉ requires M , 426.1890). The n.m.r. spectra indicated that the title compound was mainly in the enolic form, but contained 20-40% of the diketone.

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Example 30

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(piperidin-1-yl)-

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pyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-(Piperidin-1-yl)pyrimidine-5-carboxaldehyde

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5-Bromo-2-chloropyrimidine was converted to 5-bromo-2-(piperidin-1-yl)pyrimidine using the method of Nasielski et al (Tetrahedron 1972, 28, 3767). Using the method described in 21a, 5-bromo-2-(piperidin-1-yl)pyrimidine (3.63g, 15mmol) was converted to the title compound (1.23g, 10 43%); δ_H ($CDCl_3$) 1.5-1.8 (6H, m, 3',4',5'- CH_2), 3.8-4.1 (4H, m, 2 x NCH_2), 8.65 (2H, s, 4' and 6'-H), and 9.7 (1H, s, CHO).

10

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(2-(piperidin-1-yl)pyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

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Using the method described in 5a, trist trimethylsilylmonone (1.038g, 2mmol) and 2-(piperidin-1-yl)pyrimidine-5-carboxaldehyde (0.421g, 2.2mmol) were reacted to give the title compound (1.140g, 80%); δ_H (20 $CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 1.48-1.90 (9H, m, 9-H₂, 8-H, 3 x CH_2), 3.72-3.98 (7H, m, 16,13,7-H and 2 x NCH_2), 4.98-5.08 (1H, m, 1-H), and 8.30 (2H, s, 4' and 6'-H); m/z (NH₃ DCI) 710 (MH⁺, 20%), 192 (100), and 91 (82); m/z 710 (25 MH⁺, 3%), 709 (M⁺, 2), 191 (70), 129 (82), and 117 (100). (Found: M⁺, 709.3981. C₃₄H₆₃N₃O₇Si₃ requires M, 709.3974).

25

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-(piperidin-1-yl)pyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

30

Using the method described in 6b, the product from 30b (1.12g, 1.58mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 4 hours to give the title compound (0.681g, 61%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 1.5-1.9 (9H, m, 9-H₂, 8-H, 3 x CH_2), 3.7-3.95 (7H, m, 16,13,7-H and 2 x NCH_2), 6.06 (1H, s, 2-H), and 8.77 (2H, s, 4' and 6'-H); m/z (NH₃ DCI) 708 (MH⁺, 7%), 147 (97), 91 (100), and 74 (95); m/z 707 (M⁺, 1%), 190 (98), and 73 (100). (Found: M⁺, 707.3820. C₃₄H₆₁N₃O₇Si₃ requires M, 707.3817). The ¹H n.m.r.

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spectrum indicated that the title compound was essentially in the enolic form.

- 5 d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(piperidin-1-yl)-pyrimidine-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 30c (0.655g, 0.92mmol) was deprotected to give the title compound (0.388g, 85%);
10 found C, 60.72; H, 7.75; N, 8.49%. C₂₅H₃₇N₃O₇ requires C, 61.08; H, 7.59; N, 8.55%; ν_{max} (KBr) 3466, 1609, 1541, 1269, 1254, and 803cm⁻¹; λ_{max} (EtOH) 348nm (ϵ_m 33,937); δ_H (CDCl₃/CD₃OD) *inter alia* 0.93 (3H, d, J 7.1Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 1.58-1.90 (8H, m, 9-H₂ and 3 x CH₂), 3.74-4.0 (8H, m, 5,7,13,16-H and 2 x NCH₂), 6.08 (1H, s, 15 2-H), and 8.77 (2H, s, 4' and 6'-H); δ_C (CDCl₃/CD₃OD) 12.4 (C-17), 20.4 (C-14), 24.8 (C-4"), 26.0 (C-3" and 5"), 31.9 (C-9), 40.0 (C-8), 41.3 (C-4), 42.7 (C-12), 45.4 (C-2" and 6"), 55.9 (C-10), 61.1 (C-11), 65.8 (C-16), 68.7 (C-6), 70.2 (C-7), 70.6 (C-13), 74.3 (C-5), 95.6 (C-2), 116.3 (C-5'), 158.0 (C-4' and 6'), 161.9 (C-2'), 182.1 (C-1), and 190.8 (C-3); m/z 491 (M⁺, 7%), 232 (36), 206 (54), 204 (56), and 190 (100). (Found: M⁺, 491.2602. C₂₅H₃₇N₃O₇ requires M, 491.2630). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 31

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- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methyl-2-methylthio-imidazol-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

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- a) Ethyl 1-methyl-2-methylthioimidazole-4-carboxylate

Ethyl 2-mercaptopimidazole-4(5)-carboxylate (10.0g, 58mmol) was dissolved in dry DMF (200ml), and sodium hydride (80% in oil, 3.5g, 116mmol) added slowly with cooling. The mixture was stirred for 1h under argon, cooled in an ice bath, and methyl iodide (14.4ml, 232mmol) added. The reaction was then stirred overnight, diluted with water (200ml) and extracted with ethyl acetate (6 x 100ml). The combined organic extracts were washed with brine, dried and evaporated. The crude product was

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separated by flash chromatography eluting with 32-44% ethyl acetate in hexane, to give (a) the 1,2,5-isomer (3.742g, 32%), and (b) the title compound (4.261g, 37%); δ_H ($CDCl_3$) 1.35 (3H, t, J 7Hz, CH_3), 2.6 (3H, s, SCH_3), 3.6 (3H, s, NCH_3), 4.3 (2H, q, J 7Hz, CH_2), and 7.55 (1H, s, 5-H).

5 The assignments of the structures were confirmed by n.O.e. studies.

b) 1-Methyl-2-methylthioimidazole-4-carboxaldehyde

Ethyl 1-methyl-2-methylthioimidazole-4-carboxylate (1.97g, 9.8mmol) was 10 dissolved in dry THF (80ml) under argon, then diisobutylaluminium hydride (1.0M in toluene, 22ml, 22mmol) was added slowly. The mixture was stirred at room temperature for 1½h, and at reflux for ½h. The reaction was cooled, quenched with methanol (25ml) and saturated sodium sulphate (31ml), and stirred for 15 minutes. The mixture was then 15 filtered, washing well with ethyl acetate, and the filtrate extracted with ethyl acetate (x4). The combined organic extracts were dried and evaporated to give crude 4-hydroxymethyl-1-methyl-2-methylthioimidazole (1.43g, 92%).

20 This material was dissolved in dry chloroform (70ml), activated manganese dioxide (1.5g) added and the mixture stirred for 30 minutes. Only a little reaction had occurred, so 4A sieves (4g) were added, followed portionwise by more manganese dioxide (3.5g). After stirring overnight the reaction was complete. The mixture was filtered, washing the 25 manganese dioxide thoroughly with chloroform and dichloromethane, and the filtrate evaporated. The residue was purified by column chromatography on silica (38g), eluting with 90-100% ethyl acetate in hexane, to give the title compound as a white solid (1.183g, 84%; 77% overall); ν_{max} (CH_2Cl_2) 1680, 1540, 1320, and 1130cm⁻¹; δ_H ($CDCl_3$) 2.68 (3H, s, SCH_3), 3.65 (3H, s, NCH_3), 7.68 (1H, s, 5-H), and 9.7 (1H, s, CHO).

c) 3R,4R-Bistrimethylsilyloxy-2-[4-hydroxy-4-(1-methyl-2-methylthioimidazol-4-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 1-methyl-2-methylthioimidazole-4-carboxaldehyde were

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reacted to give the title compound (1.050g, 78%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 2.57 (3H, s, SCH₃), 3.58 (3H, s, NCH₃), 5.10-5.18 (1H, m, 1-H), and 6.88 (1H, s, 5'-H); m/z (NH₃ DCI) 675 (MH^+ , 40%) and 157 (100); m/z 674 (M^+ , 1%), 156 (50), 129 (62), and 117 (100). (Found: M^+ , 674.8267. C₃₀H₅₈N₂O₇SSi₃ requires M , 674.3273).

5 d) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(1-methyl-2-methylthioimidazol-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

10 Using the method described in 6b, the product from 31c (1.03g, 1.50mmol) in benzene (70ml) was reacted with manganese dioxide (2.0g) for 2 hours to give the title compound (0.656g, 64%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 2.66 (3H, s, SCH₃), 3.62 (3H, s, NCH₃), 6.44 (1H, s, 2-H), and 7.55 (1H, s, 5'-H); m/z (NH₃ DCI) 673 (MH^+ , 100%); m/z 673 (MH^+ , 2%), 672 (M^+ , 1%), 197 (30), 155 (53), 117 (50), and 73 (100). (Found: M^+ , 672.3125. C₃₀H₅₆N₂O₇SSi₃ requires M , 672.3116).

15 e) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(1-methyl-2-methylthioimidazol-4-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 5c, the product from 31d (0.240g, 0.36mmol) was deprotected to give the title compound (0.140g, 85%); ν_{max} (KBr) 3426, 1616, 1451, 1379, 1332, 1135, 1108, and 1055cm⁻¹; λ_{max} (EtOH) 328nm (ϵ_m 17,229); δ_H ($CDCl_3$) inter alia 0.93 (3H, d, J 7.1Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 2.66 (3H, s, SCH₃), 3.64 (3H, s, NCH₃), 6.44 (1H, s, 2-H), and 7.58 (1H, s, 5'-H); δ_C ($CDCl_3$) 12.6 (C-17), 16.1 (SCH₃), 20.7 (C-14), 31.6 (C-9), 33.6 (NCH₃), 39.5 (C-8), 42.2 (C-4), 42.8 (C-12), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 69.1 (C-6), 70.3 (C-7), 71.2 (C-13), 73.9 (C-5), 96.9 (C-2), 126.3 (C-5'), 137.9 (C-4'), 145.7 (C-2'), 178.5 (C-1), and 193.2 (C-3); m/z (NH₃ DCI) 457 (MH^+ , 100%); m/z 456 (M^+ , 2%), 170 (75) and 155 (100). (Found: M^+ , 456.1922. C₂₁H₃₂N₂O₇S requires M , 656.1930). The ¹H n.m.r. spectrum indicated that the title compound was mainly in the enolic form (17% of the diketone present).

Example 32

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

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a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-methoxyphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

10 Using the method described in 5a, tristrimethylsilylmonone (0.725g, 1.4mmol) and 2-methoxybenzaldehyde (218mg, 1.68mmol) were reacted to give the title compound (600mg, 65%); δ_H (CDCl₃) inter alia 0.89 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 3.83 (3H, s, OMe), 4.08-4.19 (1H, m, H-5), 5.36-5.50 (1H, m, H-1), 6.85 (1H, d, J 8.1Hz, H-3'), 6.98 (1H, t, J 7.2Hz, H-5'), 7.24 (1H, dt, J 1.6 and 8.0Hz, H-4'), 7.48 (1H, d, J 7.4Hz, H-6'). (Found: M⁺, 654.3456. C₃₂H₅₈O₈Si₃ requires M, 654.3440).

15 b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 6b, the product from 32a (600mg, 0.92mmol) in benzene (50ml) was reacted with manganese dioxide (1.5g) for 3 hours to give the title compound (260mg, 43%); δ_H (CDCl₃) inter alia 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 3.92 (3H, s, OMe), 6.53 (1H, s, 2-H), 6.96 (1H, d, J 8.3Hz, 3'-H), 7.02 (1H, t, J 7.7Hz, 5'-H), 7.43 (1H, dt, J 1.8 and 8.3Hz, 4'-H), 7.88 (1H, dd, J 1.8 and 7.8Hz, 6'-H). (Found: M⁺, 652.3293. C₃₂H₅₆O₈Si₃ requires M, 652.3283).

25 c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxyphenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

30 Using the method described in 5c, the product from 32b (250mg, 0.38mmol) was deprotected to give the title compound (142mg, 85%); ν_{max} (KBr) 3431, 1718, 1603, 1489cm⁻¹; λ_{max} (EtOH) 326.5nm (ϵ_m 12,445), 306 (11,456), 253.5 (4,740); δ_H (CDCl₃) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.92 (3H, s, OMe), 6.58 (1H, s, 2-H),

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6.97 (1H, d, J 8.3Hz, 3'-H), 7.04 (1H, t, J 7.7Hz, 5'-H), 7.45 (1H, dt, J 1.8 and 8.3Hz, 4'-H), 7.91 (1H, dd, J 1.8 and 7.8Hz, 6'-H); δ_C (CDCl₃) 12.7 (C-17), 20.7 (C-14), 31.6 (C-9), 39.5 (C-8), 42.8 (C-12), 43.3 (C-4), 55.7 (C-10), 55.7 (ArOMe), 61.3 (C-11), 65.6 (C-16), 69.3 (C-7), 70.3 (C-6), 71.3 (C-13), 73.7 (C-5), 102.4 (C-2), 111.7 (C-5'), 123.4 (C-1'), 130.2 (C-3'), 133.2 (C-6'), 158.6 (C-2'), 180.1 (C-1), 196.7 (C-3). (Found: M^+ , 437.2164. C₂₃H₃₃O₈ requires M , 437.2175). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

10 Example 33

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

15 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-methylthiophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (2.175g, 4.2mmol) and 4-methylthiobenzaldehyde (0.64ml, 4.8mmol) were reacted to give the title compound (2.12g, 75%); δ_H (CDCl₃) *inter alia* 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 2.48 (3H, s, ArSMe), 4.05-4.18 (1H, m, 5-H), 5.08-5.20 (1H, m, 1-H), 7.20-7.34 (4H, m, Ar); m/z (FAB) 693 (MNa^+).

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b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

30 Using the method described in 6b, the product from 33a (2.12g, 3.16mmol) in benzene (150ml) was reacted with manganese dioxide (4.2g) for 2 hours to give the title compound (1.3g, 62%); δ_H (CDCl₃) *inter alia* 0.89 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 2.52 (3H, s, ArSMe), 6.23 (1H, s, 2-H), 7.26 (2H, d, J 8.6Hz, 3',5'-H₂), 7.80 (2H, d, J 8.6Hz, 2',6'-H₂). (Found: M^+ , 668.3060. C₃₂H₅₆O₂SSi requires M , 668.3055).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-

hexyl)tetrahydropyran

Using the method described in 5c, the product from 33b (250mg, 0.37mmol) was deprotected to give the title compound (144mg, 85%); ν_{max} 5 (KBr) 3425, 1591, 1488, 1436, 1267cm⁻¹; λ_{max} (EtOH) 337nm (ϵ_m 27,090), 239 (5,680); δ_H (CDCl₃) *inter alia* 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 2.35 (3H, s, ArSMe), 6.23 (1H, s, 2-H), 7.26 (2H, d, J 8.6Hz, 3',5'-H₂), 7.80 (2H, d, J 8.6Hz, 2',6'-H₂); δ_C (CDCl₃) 11.9 (C-17), 14.5 (ArSMe), 20.0 (C-14), 31.5 (C-9), 39.6 (C-8), 41.9 10 (C-4), 42.3 (C-12), 55.5 (C-10), 60.7 (C-11), 65.4 (C-16), 68.3 (C-7), 69.9 (C-6), 70.3 (C-13), 73.8 (C-5), 96.6 (C-2), 125.1 (C-3',5'), 127.2 (C-2',6'), 130.5 (C-1'), 144.9 (C-4'), 181.9 (C-1), 194.1 (C-3). (Found: M^+ , 452.1867. C₂₃H₃₂O₇S requires M 452.1869). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

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Example 34

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylsulphinyl-phenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)-tetrahydropyran

Using the method described in 23, the product from 33c (200mg, 0.3mmol) was reacted to give the pure product (175mg, 85%). This material was deprotected using the method described in 5c to give the title compound 25 (154mg, 45%); ν_{max} (KBr) 3417, 1600, 1560, 1451, 1292cm⁻¹; λ_{max} (EtOH) 317nm (ϵ_m 17,420), 225 (7,480); δ_H (CDCl₃) *inter alia*, 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 2.77 (3H, s, ArS(O)Me), 6.30 (1H, s, 2-H), 7.72 (2H, d, J 8.4Hz, 3',5'-H₂), 8.03 (2H, d, J 8.4Hz, 2',6'-H₂); δ_C (CDCl₃) 12.7 (C-17), 20.6 (C-14), 31.6 (C-9), 39.6 (C-8), 42.8 30 (C-12 and C-4), 43.6 (ArS(O)Me), 55.6 (C-10), 61.1 (C-11), 65.6 (C-16), 66.8 (C-7), 70.3 (C-6), 71.2 (C-13), 73.7 (C-5), 98.0 (C-2), 123.9 (C-3',5'), 128.0 (C-2',6'), 137.2 (C-1'), 149.5 (C-4'), 180.1 (C-1), 196.7 (C-3); m/z (FAB) 491 (MNa^+), 469 (MH^+). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

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Example 35

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylsulphonyl-phenyl)-

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but-1-yl)-5S-(2S,3S-epoxy-5S-hydroxy-4S-methyl-hexyl)-
tetrahydropyran

Using the method described in 24, the product from 34c (200mg, 0.3mmol) 5 was reacted to give the pure product (155mg, 74%). This material was deprotected using the method described in 5c to give the title compound (90mg, 92%); ν_{max} (KBr) 3495, 3438, 1622, 1602cm⁻¹; λ_{max} (EtOH) 10 317.5nm (ϵ_m 14,510), 239 (8,540); δ_H (CD₃OD) *inter alia* 0.94 (3H, d, J 7.1Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 3.13 (3H, s, ArSO₂Me), 6.37 (approx. 1H, s, exch, 2-H), 7.92-8.17 (4H, m, Ar); m/z (FAB) 485 (MH^+). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 36

15

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-cyanophenyl)but-1-yl]-
5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

20

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3-cyanophenyl)-4-
hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-
4S-methylhexyl)tetrahydropyran

25

Using the method described in 5a, and on the same scale, 3-cyanobenzaldehyde (4.19mg, 3.2mmol) was reacted to give the title compound (1.46g, 80%); δ_H (CDCl₃) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 5.13-5.26 (1H, m, 1-H), 7.48-7.62 (3H, m), 7.70 (1H, s, 2'-H); m/z (NH₃ DCI), 667 (MNH_4^+ , 50%), 650 (MH^+ , 10%), 536 (100).

30

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(3-
cyanophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-
4S-methylhexyl)tetrahydropyran

35

Using the method described in 6b, the product from 36a (1.45g, 2.23mmol) in benzene (120ml) was reacted with manganese dioxide (2.18g) for 3½h to give the title compound (574mg, 40%); δ_H (CDCl₃) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 6.26 (1H, s, 2-H), 7.58 (1H, t, J 7.8Hz, 5'-H), 7.79 (1H, dd, J 1.2 and 7.7Hz, 4'-H), 8.10 (1H, dd, J 1.0 and

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6.7Hz, 6'-H), 8.16 (1H, d, J 1.4Hz, 2'-H); m/z 648 (MH^+).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-cyanophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-

5 hydropyran

Using the method described in 5c, the product from 36b (550mg, 0.85mmol) was deprotected to give the title compound (315mg, 86%); ν_{max} (KBr) 3439, 2232, 1610, 1570, 1452cm⁻¹; λ_{max} (EtOH) 312.5nm (ϵ_m 14,620),
10 239.5 (9,990); δ_H (CDCl₃) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃) 1.22 (3H, d, J 6.3Hz, 14-H₃), 6.27 (1H, s, 2-H), 7.60 (1H, t, J 7.8Hz, 5'-H), 7.80 (1H, d, with further fine coupling, J 7.8Hz, 4'-H), 8.10 (1H, d, with further fine coupling, J 8.0Hz, 6'-H), 8.16 (1H, d, J 1.2Hz, 2'-H); δ_C (CDCl₃) 12.9 (C-17), 21.0 (C-14), 31.8 (C-9), 39.9 (C-8), 42.9 (C-4), 43.0 (C-12), 55.8
15 (C-10), 61.4 (C-11), 65.8 (C-16), 69.0 (C-6), 70.5 (C-13), 71.5 (C-7), 74.1 (C-5), 98.0 (C-2), 113.3 (C-1'), 118.2 (C-3'), 129.8 (C-2'), 130.9 (C-4'), 131.3 (C-6'), 135.4 (C-5'), 136.0 (CN), 179.6 (C-3), 196.9 (C-1). (Found: M^+ 431.1949. C₂₃H₂₉NO₇ requires M 431.1944). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

20

Example 37

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-trifluoromethoxy-phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran

25

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-trifluoro-methoxyphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

30

Using the method described in 5a, tristrimethylsilylmonone (1.45mg, 2.8mmol) and 4-trifluoromethoxybenzaldehyde (608mg, 3.2mmol) were reacted to give the title compound (1.52g, 76%); δ_H (CDCl₃) inter alia 0.93 (3H, d, J 7.1Hz, 17-H₃), 1.23 (3H, d, J 6.4Hz, 14-H₃), 4.07-4.18 (1H, m, 5-H), 5.10-5.22 (1H, m, 1-H), 7.18-7.28 (2H, m, 3',5'-H₂), 7.38-7.49 (2H, m, 2',6'-H₂); m/z (NH₃ DCI) 726 (MNH_4^+ , 30%), 90 (100%). [Found: MH^+ , 709.3239. C₃₁H₅₅O₈F₃Si₃ requires MH , 709.3235.]

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b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-trifluoromethoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

- 5 Using the method described in 6b, the product from 37a (1.5g, 2.15mmol) in benzene (120ml) was reacted with manganese dioxide (3g) for 1½ hours to give the title compound (772mg, 51%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 4.08-4.20 (1H, m, 5-H), 6.24 (1H, s, 2-H), 7.22-7.34 (2H, m, 3',5'-H₂), 7.93 (2H, d, J 8.8Hz, 2',6'-H₂); m/z 707 (MH^+ , 8%), 73 (100). [Found: MH , 707.3072. $C_{31}H_{59}O_8F_3Si_3$ requires MH , 707.3079.]
- 10

- c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-trifluoromethoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran
- 15

Using the method described in 5c, the product from 37b (750mg, 1.06mmol) was deprotected to give the title compound (350mg, 74%); ν_{max} (KBr) 3496, 1624, 1583, 1506, 1441cm⁻¹; λ_{max} (EtOH) 311nm (ϵ_m 16,860), 243.5 (6730); δ_H ($CDCl_3$) *inter alia* 0.93 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 6.24 (1H, s, 2-H), 7.24-7.35 (2H, m, 3',5'-H₂), 7.92 (2H, d, J 8.8Hz, 2',6'-H₂); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.7 (C-8), 42.7 (C-4), 42.9 (C-12), 55.7 (C-10), 65.7 (C-16), 69.0 (C-7), 70.3 (C-6), 71.4 (C-13), 73.9 (C-5), 97.5 (C-2), 120.6 (C-3',5'), 129.0 (C-2',6'), 132.9 (C-1'), 152.2 (C-4'), 180.9 (C-1), 196.0 (C-3); m/z 491 (MH^+ , 30%), 189 (100). [Found: MH^+ , 491.1893. $C_{23}H_{30}O_8F_3$ requires MH , 491.1893.] The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

30 Example 38

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

- 35 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-fluorophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

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- Using the method described in 5a, tristrimethylsilylmonone (1.45g, 2.8mmol) and 4-fluorobenzaldehyde (0.34ml, 3.2mmol) were reacted to give the title compound (1.5g, 83%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 4.08-4.17 (1H, m, 5-H), 5.11-5.22 (1H, m, 1-H), 7.03 (2H, t, J 8.7Hz, 3',5'-H₂), 7.30-7.41 (2H, m, 2',6'-H₂); m/z (NH_3 DCI) 660 (MNH_4^+ , 52%), 643 (MH^+ , 15), 90 (100). [Found: MH^+ , 643.3811. $C_{31}H_{55}O_7FSi_3$ requires MH , 643.3318.]
- 5 b) $3R,4R$ -Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran
- 10 Using the method described in 6b, the product from 38a (1.5g, 2.34mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 1½ hours to give the title compound (890mg, 59%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 4.06-4.18 (1H, m, 5-H), 6.22 (1H, s, 2-H), 7.13 (2H, t, J 8.7Hz, 3',5'-H₂), 7.91 (2H, dd, J 5.4 and 8.7Hz, 2',6'-H₂); m/z (NH_3 DCI) 641 (MH^+). [Found: MH^+ , 641.3167. $C_{31}H_{54}O_7FSi_3$ requires MH , 641.3161.]
- 15 c) $3R,4R$ -Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran
- 20 Using the method described in 5c, the product from 38b (400mg, 0.625mmol) was deprotected to give the title compound (215mg, 81%); ν_{max} (KBr) 3427, 1603, 1505, 1452cm⁻¹; λ_{max} (EtOH) 310nm (ϵ_m 15,800), 248.5 (5,785); δ_H ($CDCl_3$) *inter alia* 0.93 (3H, d, J 7.1Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 6.22 (1H, s, 2-H), 7.13 (2H, t, J 8.7Hz, 3',5'-H₂), 7.90 (2H, dd, J 5.4 and 8.7Hz, 2',6'-H₂); δ_C ($CDCl_3$) 12.8 (C-17), 20.8 (C-14), 31.6 (C-9), 39.7 (C-8), 42.6 (C-4), 42.9 (C-12), 55.7 (C-10), 61.3 (C-11), 65.7 (C-16), 69.0 (C-7), 70.3 (C-6), 71.4 (C-13), 73.9 (C-5), 97.2 (C-2), 115.8 (d, J 23Hz, C-3',5'), 129.6 (d, J 9Hz, C-2',6'), 130.7 (d, J 3Hz, C-1'), 165.4 (d, J 252Hz, C-4'); 181.8 (C-1), 195.1 (C-3); m/z (NH_3 DCI) 425 (MH^+ , 15%), 79 (100). [Found: MH^+ , 425.1968. $C_{22}H_{30}O_7F$ requires MH , 425.1976.] The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 39

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3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-hydroxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-Triethylsilyloxybenzaldehyde

5

A suspension of 4-hydroxybenzaldehyde (610mg, 5mmol) in dichloromethane (30ml) at 5° under argon was treated with triethylamine (0.84ml, 6mmol) followed by triethylsilyl chloride (1ml, 6mmol). After 30 minutes ether was added and the mixture filtered through Kieselguhr.

10 The filtrate was washed with brine, dried (MgSO_4) and evaporated to give the title aldehyde (1.1g) as an orange oil; δ_{H} (CDCl_3) 0.55-1.42 (15H, m), 6.96 (2H, d, J 9Hz), 7.83 (2H, d, J 9Hz), 9.95 (1H, s). This material was sufficiently pure for further synthetic manipulations.

15 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-triethylsilyloxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 5a, 4-triethylsilyloxy-benzaldehyde (520mg, 2mmol) and tris trimethylsilylmonone (1.04g, 2mmol) were reacted to give the title compound (1.2g, 80%); δ_{H} (CDCl_3) *inter alia* 0.66-0.82 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.89 (3H, d, J 7.0Hz, 17-H₃), 0.99 (9H, t, J 7.4Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 4.08-4.17 (1H, m, 5-H), 5.05-5.16 (1H, m, 1-H), 6.84 (2H, d, J 8.5Hz, 3',5'-H₂), 7.18-7.27 (2H, m, 2',6'-H₂); m/z (FAB; 3-NOBA/Na) 777 (MNa^+ , 100%).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-triethylsilyloxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

30

Using the method described in 6b, the product from 39b (1.2g) in benzene (70ml) was reacted with manganese dioxide (3.4g) for 3 hours to give the title compound (598mg, 50%); δ_{H} (CDCl_3) *inter alia* 0.68-0.82 (6H, m, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.00 (9H, t, J 7.4Hz, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 1.20 (3H, d, J 6.4Hz, 14-H₃), 6.20 (1H, s, 2-H), 6.88 (2H, d, J 8.7Hz, 3',5'-H₂), 7.81 (2H, d, 8.7Hz, 2',6'-H₂); m/z (FAB; 3-NOBA/Na) 775 (MNa^+ , 40%), 235 (100%).

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d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-hydroxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c the product from 39c (598mg, 0.8mmol)
5 was deprotected to give the triethylsilylated title compound (264mg). This material was dissolved in tetrahydrofuran (THF) (5ml) and treated with acetic acid (30 μ l, 0.5mmol) and a solution of tetrabutylammonium fluoride trihydrate in THF (1M, 0.5ml, 0.5mmol). After 20 minutes the mixture was diluted with ethyl acetate and washed with brine, dried, evaporated
10 and chromatographed on silica eluting with dichloromethane/ methanol mixtures to give the title compound containing 25% tetrabutyl ammonium acetate (234mg). This mixture was treated with ethyl acetate (10ml), water (5ml) and nonafluorobutane sulphonate (76mg). The organic phase was separated, washed with brine, dried and evaporated.
15 Chromatography eluting with dichloromethane/methanol mixtures gave the title compound (168mg) as a solid; ν_{max} (KBr) 3385, 1604, 1508, 1455cm⁻¹; λ_{max} (EtOH) 326nm (ϵ_m 21,460); δ_{H} (d₆-acetone) *inter alia* 0.92 (3H, d, J 7.1Hz, 17-H₃), 1.16 (3H, d, J 6.4Hz, 14-H₃), 6.39 (1H, s, 2-H), 6.95 (2H, d, J 8.8Hz, 3',5'-H₂), 7.90 (2H, d, J 8.8Hz, 2',6'-H₂); δ_{C} (d₆-acetone) 12.3 (C-17), 20.8 (C-14), 32.6 (C-9), 41.2 (C-8), 42.3 (C-4), 43.3 (C-12), 55.6 (C-10), 60.4 (C-11), 66.0 (C-16), 69.4 (C-7), 70.1 (C-6), 71.1 (C-13), 75.1 (C-5), 96.7 (C-2), 116.3 (C-3',5'), 127.3 (C-1'), 130.2 (C-2',6'), 162.5 (C-4'), 184.9 (C-1), 194.1 (C-3); m/z 440 (MNH_4^+ , 12%), 423 (MH^+ , 15%), 181 (100%).
25

EXAMPLE 40

3R,4R Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-Allyloxybenzaldehyde

A solution of 4-allyloxybromobenzene (K. Mino *et al.*, Synthesis, 1979, 688)
35 (1.5g, 7.5mmol) in THF (25ml) at -70° under argon was treated with a solution of n-butyllithium in hexane (1.5M, 5ml, 7.5mmol). After 30 minutes the reaction mixture was treated with dimethylformamide (0.88ml, 11.25mmol). After 10 minutes saturated ammonium chloride was

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added and the mixture extracted with ethyl acetate. The organic phase was washed with brine, dried, evaporated and chromatographed on silica eluting with ethyl acetate/hexane mixtures to give the title compound (784mg) contaminated with ethyl acetate (16%); δ_H ($CDCl_3$) inter alia 5 4.61 (1H, dd, J 2,6Hz), 4.93 (1H, dd, J 2,14Hz), 6.71 (1H, dd, J 6,14Hz), 7.12 (2H, d, J 9Hz), 7.88 (2H, d, J 9Hz), 9.93 (1H, s). This material was used in further synthetic transformations.

10 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-allyloxyphenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, and on the same scale, the product from 15 40a was reacted to give the title compound (815mg, 43%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 4.08-4.17 (1H, m, 5-H), 4.42 (1H, d, J 6.0Hz, 2"-H), 4.75 (1H, d, J 13.7Hz, 2"-H), 6.63 (1H, dd, J 6.0, 13.7Hz, 1"-H), 6.98 (2H, d, J 8.6Hz, 3',5'-H₂), 7.32 (2H, dd, J 8.6Hz, 2',6'-H₂); m/z (NH₃DCI) 684 (MNH₄⁺, 10%), 90 (100%).

20 c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 40b (800mg, 1.2mmol) 25 in benzene (50ml) was reacted with manganese dioxide (1.2g) for 3 hours to give the title compound (437mg, 55%); δ_H ($CDCl_3$) inter alia 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.2Hz, 14-H₃), 4.08-4.17 (1H, m, 5-H), 4.56 (1H, d, J 6.0Hz, 2"-H), 4.89 (1H, d, J 13.6Hz, 2"-H), 6.21 (1H, s, 2-H), 6.68 (1H, dd, J 6.0, 13.6Hz, 1"-H), 7.09 (2H, d, J 8.7Hz, 3',5'-H₂), 7.88 (2H, d, J 8.7Hz, 2',6'-H₂); m/z (FAB; 3-NOBA/Na) 687 (MNa⁺, 18%), 117 (30 100%).

d) 3R,4R-Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

35 Using the method described in 5c, the product from 40c (370mg, 0.56mmol) was deprotected to give the title compound (218mg, 87%); ν_{max} (KBr) 3436, 1600, 1502, 1440cm⁻¹; λ_{max} (EtOH) 323nm (ϵ_m 22620); δ_H ($CDCl_3$) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-

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H₃), 4.59 (1H, dd, J 1.8, 6.1Hz, 2"-H), 4.91 (1H, dd, J 1.8, 13.6Hz, 2"-H), 6.22 (1H, s, 2-H), 6.69 (1H, dd, J 6.0, 13.6Hz, 1"-H), 7.05 (2H, d, J 8.8Hz, 3',5'-H₂), 7.88 (2H, d, J 8.8Hz, 2',6'-H₂); δ_C (CDCl₃) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.7 (C-8), 42.5 (C-4), 42.6 (C-12), 55.7 (C-10), 61.3 (C-11), 5 65.7 (C-16), 69.1 (C-7), 70.3 (C-6), 71.3 (C-13), 73.9 (C-5), 96.7 (C-2), 97.4 (C-2"), 116.5 (C-3',5'), 129.0 (C-1'), 129.3 (C-2',6'), 146.7 (C-1"), 160.2 (C-4'), 182.3 (C-1), 194.7 (C-3). [Found: M⁺ 448.2119. C₂₄H₃₂O₈ requires M 448.2097]. The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

10

EXAMPLE 41

15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethyloxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-methoxymethyloxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

20

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 4-methoxymethyloxobenzaldehyde (J.P. Yardley *et al*, Synthesis, 1976, 244) (365mg, 2.2mmol) was reacted to give the title compound (1.25g, 91%); δ_H (CDCl₃) *inter alia* 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 3.47 (3H, s, OMe), 4.02-4.18 (1H, m, 5-H), 5.03-5.15 (1H, m, 1-H), 5.17 (2H, s, OCH₂O), 7.02 (2H, d, J 8.7 Hz, 3',5'-H₂), 7.22-7.32 (2H, m, 2',6'-H₂); *m/z* (NH₃, DCI), 702 (MNH₄⁺, 8%), 239 (100%).

30 b) 3R,4R-Bistrimethylsilyloxy-2S[2,4-dioxo-4-(4-methoxymethyl-oxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 41a (1.2g, 1.75mmol) in benzene (50ml) was reacted with manganese dioxide (1.8g) for 3^{1/2} hours to give the title compound (750mg, 62%); δ_H (CDCl₃) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.49 (3H, s, OMe), 5.23 (2H, s, OCH₂O), 6.21 (1H, s, 2-H), 7.07 (2H, d, J 8.9Hz, 3',5'-H₂), 7.86

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(2H, d, J 8.9Hz, 2',6'-H₂); m/z (NH₃, DCI) 683 (MNH₄⁺, 15%), 90 (100%).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

5

Using the method described in 5c, the product from 41b (750mg) was deprotected to give the title compound (400mg, 78%); ν_{max} (KBr) 3421, 1602, 1507, 1454cm⁻¹; λ_{max} (EtOH) 321.5nm (ϵ_m 20,160); δ_{H} (CDCl₃) inter alia 0.94 (3H, d, J 7.1Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 3.49 (3H, s, OMe), 5.24 (2H, s, OCH₂O), 6.21 (1H, s, 2-H), 7.08 (2H, d, J 8.9Hz, 3',5'-H₂), 7.86 (2H, d, J 8.9Hz, 2',6'-H₂); δ_{C} (CDCl₃) 12.8 (C-17), 20.8 (C-14), 31.7 (C-9), 39.7 (C-8), 42.7 (C-4), 42.9 (C-12), 55.8 (C-10), 56.3 (OMe), 65.7 (C-11), 69.2 (C-7), 70.3 (C-6), 71.4 (C-13), 73.7 (C-5), 94.2 (OCH₂O), 96.7 (C-2), 116.1 (C-3',5'), 127.9 (C-1'), 129.2 (C-2',6'), 160.9 (C-4'), 182.7 (C-1), 194.4 (C-3); (Found: M⁺ 466.2198. C₂₄H₃₄O₉ requires M 466.2203). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

20 EXAMPLE 42

3R,4R-Dihydroxy-2S-[4-(but-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

25

a) 2-[3R,4R-Bistrimethylsilyloxy-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran-2S-yl]methylprop-2-ene-1-yl but-1-yl ketone

30

A 1.75:1 mixture of the product from 1a (900mg, 1.5mmol) in THF (20ml) under argon at -70° was treated dropwise with a solution of n-butyllithium in hexane (1.5M, 2ml, 3mmol). After 30 minutes the mixture was worked-up and purified as in 1b to give material containing the title compound (320mg); δ_{H} (CDCl₃) inter alia 3.16 (2H, s, 2-H₂), 4.90 (1H, s, 15-H), 5.03 (1H, s, 15-H).

35

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(but-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethyl-silyloxy-4S-methylhexyl)tetrahydropyran

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The material from 41a (300mg) in dichloromethane (20ml) was ozonolysed and then purified as described in 1c to give the title compound (93mg, 50%); δ_H ($CDCl_3$) inter alia 1.20 (3H, d, J 6.3Hz, 14-H₃), 5.59 (1H, s, 2-H).

5 c) 3R,4R-Dihydroxy-2S[4-(but-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetra-hydropyran

Using the method described in 5c, the product from 41b (85mg, 0.14mmol) was deprotected to give the title compound (43mg, 78%); ν_{max} (KBr) 3460, 10 1622, 1459cm⁻¹; λ_{max} (EtOH) 276nm (ϵ_m 9,295); δ_H ($CDCl_3$) inter alia 1.20 (3H, d, J 6.3Hz, 14-H₃), 5.60 (1H, s, 2-H); m/z (NH₃, DCI) 387 (MH^+ , 100%). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

15 EXAMPLE 43

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-hydroxyethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

20 a) 4-(2-Triethylsilyloxyethoxy)benzaldehyde

A solution of 4-(2-hydroxyethoxy)benzaldehyde (J. Bernstein et al, JACS, 1951, 73, 906) (996mg, 6mmol) in dichloromethane (20ml) under argon at 5° was treated with triethylamine (1.17ml, 8.4mmol) followed by 25 triethylsilyl chloride (1.21ml, 7.2mmol). After 30 minutes the mixture warmed to room temperature and after a further 30 minutes ether was added and the mixture was washed with 5% citric acid, saturated sodium bicarbonate and brine then dried and evaporated to give the crude title compound (1.53g, 91%); δ_H ($CDCl_3$) 0.64 (6H, q, J 7.8Hz), 0.98 (9H, t, J 7.8Hz), 4.00 (2H, t, J 5.1Hz), 4.14 (2H, t, J 5.1Hz), 7.02 (2H, d, J 8.7Hz), 30 7.83 (2H, d, J 8.7Hz), 9.90 (1H, s).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(2-triethylsilyloxyethoxy)phenyl]but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and the product from 43a (560mg, 2mmol) were reacted to give the

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title compound (1.33g, 83%); δ_H ($CDCl_3$) 0.64 (6H, q, J 8.0Hz, $SiCH_2$),
0.90 (3H, d, J 7.0Hz, 17-H₃), 0.98 (9H, t, J 8.0Hz, $SiCH_2Me$), 1.18 (3H, d,
 J 6.3Hz, 14-H₃), 5.07-5.18 (1H, m, 1-H), 6.89 (2H, d, J 8.6Hz, 3',5'-H₂),
7.28 (2H, d, J 8.6Hz, 2',6'-H₂); m/z (NH₃.DCI) 816 (MNH_4^+ , 5%), 90
5 (100%).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-[2-triethyl-
silyloxyethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-
methylhexyl)tetrahydropyran

10

Using the method described in 6b, the product from 43b (1.3g, 1.63mmol)
in benzene (70ml) was reacted with manganese dioxide (2.7g) for 3 $\frac{1}{2}$
hours to give the title compound (713mg, 55%); δ_H ($CDCl_3$) inter alia 0.65
(6H, q, J 7.9Hz, $Si(CH_2Me)_3$), 0.90 (3H, d, J 7.0Hz, 17-H₃), 0.98 (9H, t, J
15 8.0Hz, $Si(CH_2Me)_3$), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.12 (2H, t, J 4.9Hz, 1"-
H₂), 6.20 (1H, s, 2-H), 6.95 (2H, d, J 8.7Hz, 3',5'-H₂), 7.87 (2H, d, J 8.7Hz,
2',6'-H₂); m/z (FAB: thioglycerol) 797 (MH^+ , 10%), 157 (100%).

20

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-hydroxyethoxy]phenyl)buty-
1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

25

Using the method described in 5c, the product from 43c (700mg,
0.88mmol) was deprotected to give the title compound (294mg, 72%); ν_{max}
(KBr) 3421, 1603, 1508, 1451cm⁻¹; λ_{max} (EtOH) 324.5nm (ϵ_m 20,790); δ_H
($CDCl_3/d_4$ -MeOH) inter alia 0.93 (3H, d, J 7.1Hz, 17-H₃), 1.21 (3H, d, J
6.3Hz, 14-H₃), 4.14 (2H, t, J 4.8Hz, 1"-H₂), 6.23 (approx. 1H, s, 2-H), 6.98
(2H, d, J 8.9Hz, 3',5'-H₂), 7.86 (2H, d, J 8.9Hz, 2',6'-H₂); δ_c ($CDCl_3/d_4$ -
MeOH) 12.3 (C-17), 20.3 (C-14), 31.5 (C-9), 39.6 (C-8), 41.7 (C-4), 42.5 (C-
12), 55.6 (C-10), 60.9 (C-11), 65.4 (C-2"), 68.6 (C-7), 69.5 (C-1"), 70.1 (C-6),
30 70.7 (C-13), 73.9 (C-5), 96.4 (C-2), 114.4 (C-3',5'), 127.1 (C-1'), 129.1 (C-
2',6'), 162.3 (C-4'), 182.7 (C-1), 193.5 (C-3); m/z (FAB: Glycerol) 467 (MH^+ ,
30%), 185 (100%). The ¹H n.m.r. spectrum indicated that the title
compound was essentially in the enolic form.

35

EXAMPLE 44

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-fluorophenyl)but-1-yl]-5S-(2S,3S-
epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

5 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3-fluorophenyl)-4-hydroxy-2-
oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methyl-
hexyl)tetrahydropyran

10 Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and 3-fluorobenzaldehyde (0.23ml, 2.2mmol) were reacted to give the title compound (0.998g, 78%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 5.08-5.24 (1H, m, 1-H), 6.91-7.37 (4H, m, 2',4',5',6'-H₄); (Found M^+ 642.8237. $C_{31}H_{55}O_3FSi_3$ requires 642.3240).

15 b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(3-fluorophenyl)but-1-
yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran
15 Using the method described in 6b, the product from 44a (0.99g, 1.5mmol) in benzene (70ml) was reacted with manganese dioxide (2.0g) for 3 $\frac{1}{2}$ hours to give the title compound (489mg, 49%); δ_H ($CDCl_3$) *inter alia* 0.91 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.4Hz, 14-H₃), 6.24 (1H, s, 2-H), 7.16-7.26 (1H, m, 3'-H), 7.37-7.48 (1H, m, 4'-H), 7.58-7.71 (2H, m, 2',6'-H₂); m/z (NH₃.DCI) 641 (MH^+ , 30%), 90 (100%).

25 c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(3-fluorophenyl)but-1-yl]-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran
25 Using the method described in 5c, the product from 44b (480mg) was deprotected to give the title compound (229mg, 76%); ν_{max} (KBr) 3423, 1581, 1455, 1380cm⁻¹; λ_{max} (EtOH) 312nm (ϵ_m 15,735); δ_H ($CDCl_3$) *inter alia* 0.94 (3H, d, J 6.9Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 6.24 (1H, s, 2-H), 7.17-7.69 (4H, m, 2',4',5',6'-H₄); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.6 (C-8), 42.7 (C-4), 42.8 (C-12), 55.6 (C-10), 61.2 (C-11), 65.6 (C-16), 68.9 (C-6), 70.2 (C-7), 71.3 (C-13), 73.8 (C-5), 97.7 (C-2), 113.8 (d, J 43.3Hz, C-4'), 119.3 (d, J 21.2Hz, C-2'), 122.7 (C-6'), 130.2 (d, 7.9Hz, C-5'), 136.6 (d, J 7.1Hz, C-1'), 162.8 (d, J 247.3Hz, C-3'); 180.6 (C-1), 191.3 (C-3).
35 (Found: M^+ 424.1898. $C_{22}H_{29}O_7F$ requires M 424.1897). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 45

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

5

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-fluorophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

10 Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and 2-fluorobenzaldehyde (0.23ml, 2.2mmol) were reacted to give the title compound (850mg, 66%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.06-4.19 (1H, m, 5-H), 5.40-5.50 (1H, m, 1-H), 6.87-7.06 (1H, m, 5'-H), 7.14-7.32 (2H, m, 4',6'-H₂), 15 7.52-7.60 (1H, m, 3'-H); m/z ($NH_3.DCI$) 660 (MMH_4^+ , 15%), 90 (100%).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 6b, the product from 45a (730mg) in benzene (50ml) was reacted with manganese dioxide (1.65g) for 3 $\frac{1}{2}$ hours to give the title compound (480mg, 67%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 6.38 (1H, d, J 1.2Hz, 2-H), 7.07-7.18 (1H, m, Ar-H), 7.20-7.26 (1H, m, Ar-H), 7.42-7.53 (1H, m, Ar-H), and 7.90-7.99 (1H, m, Ar-H); m/z 640 (M^+ , 0.5%), 625(1), 165(53), 25 117(92), and 73(100). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

30 Using the method described in 5c, the product from 45b (0.110g, 0.17mmol) was deprotected to give the title compound (0.053g, 67%); ν_{max} (KBr) 1610, 1587, 1459, 1112, 1043, and 771cm⁻¹; λ_{max} (EtOH) 312nm (em 15,920); δ_H ($CDCl_3$) *inter alia* 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 6.39 (1H, s, 2-H), 7.08-7.30 (2H, m, 2Ar-H), 7.42-7.55 (1H, m, Ar-H), and 7.87-7.99 (1H, m, Ar-H); m/z ($NH_3.DCI$) 442 (MNH_4^+ , 10%), 425 (MH^+ , 18), and 156 (100); m/z (FAB, 3-NOBA/Na) 447 (MNa^+).

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The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 46

5

3R,4R-Dihydroxy-2S-[4-(3,4-difluorophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

- 10 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3,4-difluorophenyl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

15 Using the method described in 5a, tristrimethylsilylmonone (1.04g, 2mmol) and 3,4-difluorobenzaldehyde (0.24ml, 2.2mmol) were reacted to give the title compound (0.880g, 66%); δ_{H} (CDCl_3) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 5.07-5.17 (1H, m, 1-H), and 7.01-7.30 (3H, m, Ar-H); m/z 660 (M^+ , 0.5%), 129 (46), 117 (85), and 73 (100).

- 20 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(3,4-difluorophenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

25 Using the method described in 6b, the product from 46a (1.39g) in benzene (100ml) was reacted with manganese dioxide (2.5g) for 3½ hours to give the title compound (780mg, 57%); δ_{H} (CDCl_3) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 6.20 (1H, s, 2-H), 7.17-7.29 (1H, m, Ar-H), and 7.61-7.78 (2H, m, Ar-H); m/z 658 (M^+ , 0.5%), 643(1), 117(73), and 73(100); m/z (FAB 3-NOBA/Na) 703 (M-H+2Na⁺) and 681 (MNa⁺). The ^1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

35

c) 3R,4R-Dihydroxy-2S-[4-(3,4-difluorophenyl)-2,4-dioxo-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 46b (385mg, 0.58mmol) was deprotected to give the title compound (226mg, 87%); ν_{max} (KBr) 1612, 1594, 1515, 1280, 1118, 1090, and 1043cm⁻¹; λ_{max} (EtOH)

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311.5nm (em 14,940); δ_H ($CDCl_3$) *inter alia* 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 6.19 (1H, s, 2-H), 7.19-7.31 (1H, m, Ar-H), and 7.61-7.78 (2H, m, Ar-H); δ_c ($CDCl_3$) 12.2 (C-17) 20.2 (C-14), 31.6 (C-9), 39.8 (C-8), 41.9 (C-4), 42.5 (C-12), 55.7 (C-10), 60.9 (C-11), 65.6 (C-16), 68.5 (C-6), 70.0 (C-7), 70.5 (C-13), 74.0 (C-5), 97.2 (C-2), 116.3 (J 19Hz) and 117.5 (J 18Hz) (C-2' and 5'), 123.8 (C-6'), 131.8 (C-1'), 149.8 and 153.0 (two overlapping dd, J 253 and 13Hz, C-3' and 4'), 180.4 (C-1), and 194.5 (C-3); m/z (FAB 3-NOBA/Na) 487 ($M-H+2Na^+$) and 465 (MNa^+); m/z (FAB Thioglycerol) 460 (MNH_4^+) and 443 (MH^+). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

EXAMPLE 47

15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-N-(2-hydroxyethyl)-N-methylaminopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 5-Bromo-2-N-(2-hydroxyethyl)-N-methylaminopyridine

20 2,5-Dibromopyridine (4.74g, 20mmol) in 2-(methylamino)ethanol (5ml, 62mmol) was heated at 95-110°C for 6h, and stirred at RT for 16h. The viscous oil was then diluted with water (30ml) and extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed with brine, dried and evaporated to give a pale yellow viscous oil (4.565g, 99%);
25 δ_H ($CDCl_3$) 3.05 (3H, s, NCH₃), 3.70 (2H, t, J 4.7Hz, CH₂), 3.84 (2H, t, J 4.7Hz, CH₂), 4.27 (1H, br, OH, xch + D₂O), 6.45 (1H, d, J 9.0Hz, 3-H), 7.52 (1H, dd, J 9.0 and 2.5Hz, 4-H), and 8.08 (1H, d, J 2.4Hz, 6-H); m/z 232/230 (M^+ , 18%) and 201/199 (100). (Found: M^+ , 230.0056. C₈H₁₁BrN₂O requires M , 230.0055).

30 b) 5-Bromo-2-N-methyl-N-(2-triethylsilyloxyethyl)amino pyridine

35 5-Bromo-2-N-(2-hydroxyethyl)-N-methylaminopyridine (4.53g, 19.6mmol) was dissolved in dry dichloromethane (70ml), cooled in an ice bath, and treated with triethylamine (3.8ml, 27mmol) and chlorotriethylsilane (3.95ml, 23.5mmol). After five minutes the mixture was diluted with ether, filtered and evaporated. The residue was purified by column chromatography on silica (47g), eluting with 3-5% ethyl acetate in hexane,

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to give the pure product as a colourless oil (6.510g, 96%); δ_H ($CDCl_3$) 0.5-0.62 (6H, m, 3xSiCH₂), 0.88-0.96 (9H, m, 3xCH₃), 3.08 (3H, s, NCH₃), 3.64 (2H, d, J 5.8Hz, CH₂), 3.78 (2H, d, J 5.7Hz, CH₂), 6.42 (1H, d, J 9.1Hz, 3-H), 7.47 (1H, dd, J 9.1 and 2.5Hz, 4-H), and 8.13 (1H, d, J 2.5Hz, 5-H); m/z 347/345 (MH^+ , 40%), 346/344 (M^+ , 50), and 201/199(100). (Found: M^+ , 344.0919. $C_{14}H_{25}BrN_2OSi$ requires M , 344.0920).

c) 2-N-Methyl-N-(2-triethylsilyloxyethyl)aminopyridine-5-carboxaldehyde

5-Bromo-2-N-methyl-N-(2-triethylsilyloxyethyl)aminopyridine (1.727g, 5mmol) was dissolved in dry THF (30ml), cooled to -90°C, and treated dropwise with n-butyllithium (1.5M, 3.67ml, 5.5mmol). The mixture was stirred at -95°C for five minutes, then N,N-dimethylformamide (1.16ml, 15mmol) added. Stirring was continued for 3/4h at -90°C, then the reaction was quenched with saturated ammonium chloride. Water was added, and the mixture extracted with ethyl acetate (x3). The combined organic extracts were washed with brine, dried and evaporated. The crude product was purified by column chromatography, eluting with 10-15% ethyl acetate in hexane, to give the title compound as a pale yellow oil (1.354g, 92%); δ_H ($CDCl_3$) 0.56 (6H, q, J 7.9Hz, 3xSiCH₂), 0.92 (9H, t, J 7.9Hz, 3-H), 3.21 (3H, s, NCH₃), 3.72-3.88 (4H, m, 2 x CH₂), 6.58 (1H, d, J 9.0Hz, 3-H), 7.90 (1H, dd, J 9.0 and 2.2Hz, 4-H), 8.53 (1H, d, J 2.2Hz, 6-H), and 9.76 (1H, s, CHO); m/z 295 (MH^+ , 60%), 294 (M^+ , 55), 163 (70), 25 and 136 (100). (Found: M^+ , 294.1767. $C_{15}H_{26}N_2O_2Si$ requires M , 294.1764).

d) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-N-methyl-N-(2-triethylsilyloxyethyl)aminopyrid-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-N-methyl-N-(2-triethylsilyloxyethyl)aminopyridine-5-carboxaldehyde (0.647g, 2.2mmol) were reacted to give the title compound (1.353g, 83%); δ_H ($CDCl_3$) inter alia 0.52-0.64 (6H, m, 3xSiCH₂), 0.88-0.98 (12H, m, 4xCH₃), 3.11 (3H, s, NCH₃), 5.01-5.12 (1H, m, 1-H), 6.53 (1H, br d, 3'-H), 7.50 (1H, br d, 4'-H), and 8.09 (1H, d, J 2.2Hz, 6'-H); m/z (FAB, 3NOBA/Na) 835 (MNa^+) and 813 (MH^+).

5 e) 3R,4R-Bristrimethylsilyloxy-2S-[2,4-dioxo-4-(2-N-methyl(2-triethylsilyloxyethyl)aminopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

10 Using the method described in 6b, the product from 47d (1.331g, 1.64mmol) in benzene (70ml) was reacted with manganese dioxide (4.1g) for 5h to give the title compound (0.631g, 48%); δ_H ($CDCl_3$) *inter alia* 0.5-0.63 (6H, m, 3xSiCH₂), 0.87-0.97 (12H, m, 4xCH₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.19 (3H, s, NCH₃), 6.13 (1H, s, 2-H), 6.55 (1H, br d, 3'-H), 7.95 (1H, dd, J 9.1 and 2.1Hz, 4'-H), and 8.70 (1H, d, J 2.2Hz, 6'-H); m/z 810 (M⁺, 1%) 293(40), 135(45), 117(78), and 73(100). (Found: M⁺, 810.4524. C₃₉H₇₄N₂O₈Si₄ requires M, 810.4522). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

15 f) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-N-(2-hydroxyethyl)-N-methylaminopyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 5c, the product from 47e (0.610g, 0.75mmol) was completely deprotected to give the title compound (0.325g, 90%); ν_{max} (KBr) 3423, 1603, 1521, 1403, 1279, 1111, and 1054cm⁻¹; λ_{max} (EtOH) 356nm (ϵ_m 32,162); δ_H ($CDCl_3/CD_3OD$) *inter alia* 0.92 (3H, d, J 7.1Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 3.16 (3H, s, NCH₃), 6.14 (1H, s, 2-H), 6.58 (1H, d, J 9.1Hz, 3'-H), 7.96 (1H, dd, J 9.1 and 2.4Hz, 4'-H), and 8.63 (1H, d, J 2.4Hz, 6'-H); δ_C ($CDCl_3/CD_3OD$) 12.5 (C-17), 20.5 (C-14), 31.8 (C-9), 37.9 (NCH₃), 39.8 (C-8), 41.5 (C-4), 42.7 (C-12), 53.4 (NCH₃), 55.8 (C-10), 61.1 (C-11), 61.2 (OCH₂), 65.7 (C-16), 68.7 (C-6), 70.2 (C-7), 70.8 (C-13), 74.2 (C-5), 95.8 (C-2), 105.9 (C-4'), 119.0 (C-5'), 148.7 (C-6'), 160.8 (C-2'), 183.1 (C-1), and 191.4 (C-3); m/z 480 (M⁺, 2%) and 163 (100). (Found: M⁺, 480.2471. C₂₄H₃₆N₂O₈ requires M, 480.2472). The n.m.r. spectra indicated that the title compound was mainly in the enolic form.

35 EXAMPLE 48

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(4-hydroxypiperidin-1-yl)pyrid-5-yl)but-1-yl]-5S-[2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 5-Bromo-2-(4-hydroxypiperidin-1-yl)pyridine

2,5-Dibromopyridine (3.554g, 15mmol) and 4-hydroxypiperidine (4.552g, 5 45mmol) were heated at 100-110°C for 1h. The mixture was diluted with water and extracted with ethyl acetate (3x40ml). The combined organic extracts were dried and evaporated to give a white solid, which was recrystallised from chloroform/ hexane to give the title compound as white crystals (3.058g, 79%); m.p. 98.5-99.5°C; found C, 46.66; H, 5.10; N, 10.89%. $C_{10}H_{13}BrN_2O$ requires C, 46.71; H, 5.10; N, 10.89%; δ_H ($CDCl_3$) 1.48-1.66 (3H, m, 3'-H, 5'-H, OH), 1.90-2.05 (2H, m, 3'-H, 5'-H), 3.10-3.25 (2H, m, 2'-H, 6'-H), 3.87-4.06 (3H, m, 2'-H, 4'-H, 6'-H), 6.58 (1H, d, J 9.1Hz, 3-H), 7.52 (1H, dd, J 9.1 and 2.5Hz, 4-H), and 8.17 (1H, d, J 2.4Hz, 6'-H; m/z 258/256, 213/211 (90), 201/199 (80), 187/185 (85), and 157/159 (69). (Found: (M^+ , 256.0216. $C_{10}H_{13}BrN_2O$ requires M , 256.0211).

b) 5-Bromo-2-(4-trimethylsilyloxy)piperidin-1-yl)pyridine

20 5-Bromo-2-(4-hydroxypiperidin-1-yl)pyridine (2.985g, 11.6mmol) was dissolved in dry dichloromethane (40ml), cooled in an ice bath, and treated with triethylamine (2.1ml, 15mmol) and chlorotrimethylsilane (1.76ml, 14mmol). After $1/2$ h the mixture was diluted with ether, filtered and evaporated. The residue was redissolved in ether, filtered and evaporated to give an off-white crystalline solid (3.797g, 99%); δ_H ($CDCl_3$) 0.14 (9H, s, $Si(CH_3)_3$), 1.49-1.66 (2H, m, 3'-H, 5'-H), 1.75-1.90 (2H, m, 3'-H, 5'-H), 3.11-3.25 (2H, m, 2'-H, 6'-H), 3.82-3.99 (3H, m, 2'-H, 4'-H, 6'-H), 6.57 (1H, d, J 9.1Hz, 3-H), 7.50 (1H, dd, J 9.1 and 2.5Hz, 4-H), and 8.17 (1H, d, J 2.4Hz, 6-H); m/z 330/328 (M^+ , 80%), 211/213 (100), and 73(74). (Found: 25 M^+ , 328.0606. $C_{13}H_{21}BrN_2OSi$ requires M , 328.0607).

c) 2-(4-Trimethylsilyloxy)piperidin-1-yl)pyridine-5-carboxaldehyde

35 Using the method described in 47c, 5-bromo-2-(4-trimethylsilyloxy-piperidin-1-yl)pyridine (1.647g, 5mmol) was reacted to give the title compound as yellow crystals (0.932g, 67%); δ_H ($CDCl_3$) 0.15 (9H, s, $Si(CH_3)_3$), 1.51-1.69 (2H, m, 3'-H, 5'-H), 1.77-1.92 (2H, m, 3'-H, 5'-H), 3.44-3.58 (2H, m, 2'-H, 6'-H), 3.92-4.13 (3H, m, 2'-H, 4'-H, 6'-H), 6.68 (1H,

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d, J 9.1Hz, 3-H), 7.91 (1H, dd, J 9.1 and 2.3Hz, 4-H), 8.54 (1H, d, J 2.3Hz, 6-H), and 9.76 (1H, s, CHO); m/z 278 (M^+ , 60%), 263 (38), 209 (78), 161 (100), and 107 (69). (Found: M^+ , 278.1454. $C_{14}H_{22}N_2O_2Si$ requires M , 278.1451).

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d) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-(4-trimethylsilyloxy)piperidin-1-yl)pyrid-5-yl]-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

10 Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-(4-trimethylsilyloxy)piperidin-1-yl)pyridine-5-carboxaldehyde (0.613g, 2.2mmol) were reacted to give the title compound (1.135g, 71%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 5.02-5.15 (1H, m, 1-H), 6.68 (1H, br d, 3'-H), 7.53 (1H, br d, 4'-H), 15 and 8.13 (1H, d, J 2.2Hz, 6'-H); m/z (NH_3 , DCI) 797 (MH^+ , 15%) and 279 (100); m/z 796 (M^+ , 0.2%), 278(31), 129(74), and 73(100). (Found: M^+ , 796.4364. $C_{38}H_{72}N_2O_8Si_4$ requires M , 796.4366).

20 e) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-(4-trimethylsilyloxy)piperidin-1-yl)pyrid-5-yl]but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 48d (1.120g, 1.4mmol) in benzene (70ml) was reacted with manganese dioxide (2.9g) for 3h to give the title compound (0.633g, 57%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 6.13 (1H, s, 2-H), 6.6-6.72 (1H, m, 3'-H), 7.95 (1H, br d, 4'-H), and 8.70 (1H, d, J 2.3Hz, 6'-H); m/z (NH_3 DCI) 795 (MH^+ , 15%), 251(32), 92(52), and 90(100); m/z 794 (M^+ , 0.5%), 277 (100), 117 (76), and 73 (96). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

f) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(4-hydroxypiperidin-1-yl)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

35 Using the method described in 5c, the product from 48e (0.600g, 0.75mmol) was completely deprotected to give the title compound (0.240g, 63%); m.p. 137-138°C (chloroform/ethyl acetate/hexane); ν_{max} (KBr)

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3453, 1608, 1500, 1440, 1357, 1250, and 1075cm⁻¹; λ_{max} (EtOH) 358nm (ϵ_m 38,099); δ_H (CD₃OD) *inter alia* 0.94 (3H, d, J 7.2Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 1.34-1.58 (3H, m, 12-H, 3"-H, 5"-H), 1.86-2.02 (3H, m, 8-H, 3"-H, 5"-H), 4.15-4.28 (2H, m, 2"-H), 6"-H), 6.26 (1H, s, 2-H), 6.85
5 (1H, d, J 9.2Hz, 3'-H), 7.99 (1H, dd, J 9.2 and 2.4Hz, 4'-H), and 8.67 (1H, d, J 2.3Hz, 6'-H); δ_C (CD₃OD) 12.2 (C-17), 20.2 (C-14), 32.9 (C-9), 34.7 (C-3" and 5"), 41.6 (C-8), 42.0 (C-4), 43.5 (C-2" and 6"), 43.7 (C-12), 56.8 (C-10), 61.2 (C-11), 66.3 (C-16), 68.3 (C-4"), 69.8 (C-6), 70.6 (C-13), 71.5 (C-7), 75.5 (C-5), 96.6 (C-2), 107.1 (C-4'), 120.1 (C-5'), 137.4 (C-3'), 149.9 (C-6'),
10 161.5 (C-2'), 184.4 (C-1), and 192.4 (C-3); *m/z* 506 (M^+ , 5%), 247(20), 220(29), and 205(100). (Found: M^+ , 506.2624. C₂₆H₃₈N₂O₈ requires M , 506.2628). A further quantity of the title compound (0.096g, 25%) was obtained after chromatography of the mother liquors. The n.m.r. spectra indicated that the compound was essentially in the enolic form.

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EXAMPLE 49

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(3-hydroxyprop-1-oxy)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

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a) 3-Iodo-1-triethylsilyloxypropane

3-Bromopropan-1-ol (1.81ml, 20mmol) and sodium iodide (6.75g, 45mmol) in acetone (15ml) were refluxed for 1 $\frac{1}{2}$ h. The mixture was cooled, 25 filtered and reduced in volume. Water was added and the mixture extracted with ether. The combined organic extracts were washed with sodium metabisulphite solution and brine, dried and evaporated. The residue was distilled, using a water pump (15mm Hg), to give 3-iodopropan-1-ol (2.885g, 78%) b.p. 96-100°C; δ_H (CDCl₃) 2.04 (2H, q, J 7Hz, 2-H₂), 3.15 (1H, s, OH), 3.3 (2H, t, J 7Hz, 1-H₂), and 3.7 (2H, t, J 7Hz, 3-H₂).

3-Iodopropan-1-ol (2.79g, 15mmol) was dissolved in dry dichloromethane (30ml), cooled in an ice bath, and treated with triethylamine (2.8ml, 35 20mmol) and chlorotriethylsilane (3ml, 17.8mmol). After 1/2h the mixture was diluted with ether, filtered and carefully evaporated to give the title compound, which was used without further purification.

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b) Ethyl 2-(3-triethylsilyloxyprop-1-oxy)pyridine-5-carboxylate

A suspension of ethyl 2-hydroxypyridine-5-carboxylate (1.170g, 7mmol) and silver carbonate (1.930g, 7mmol) in benzene (30ml) was stirred with 5 3-iodo-1-triethylsilyloxypropane (15mmol) for 23h. T.l.c. showed little or no reaction, so more benzene was added and the mixture gently refluxed for 48h, then stirred at room temperature for a further 48h. The mixture was then filtered and evaporated. The crude product was separated by column chromatography, eluting with 0-20% ethyl acetate in hexane, to 10 give: (a) recovered 3-iodo-1-triethylsilyloxypropane (1.33g, 4.4mmol); (b) the title compound (contaminated with a little of (a)) (1.55g, ca.65%); δ_H ($CDCl_3$) 0.53-0.69 (6H, m, 3xSiCH₂), 0.89-1.01 (9H, m, 3xCH₃), 1.39 (3H, t, J 7.1Hz, CH₃), 2.01 (2H, q, J 6.2Hz, 2'-H₂), 3.79 (2H, t, J 6.2Hz, 3'-CH₂), 4.37 (2H, q, J 7.1Hz, CO₂CH₂), 4.46 (2H, t, J 6.2Hz, 1'-H₂), 6.74 15 (1H, d, J 8.9Hz, 3-H), 8.15 (1H, dd, J 8.8 and 2.4Hz, 4-H), and 8.82 (1H, d, J 2.4Hz, 67-H); m/z (NH₃ DCI) 340 (MH^+ , 100%); m/z 339 (M^+ , 0.5%), 310(91), 252(100), and 224(45). (Found: M^+ , 339.1863. C₁₇H₂₄NO₄Si requires M , 339.1866); and (c) the N-alkylated compound (0.56g, 24%).

20 c) 2-(3-Triethylsilyloxyprop-1-oxy)pyridine-5-carboxaldehyde

Ethyl 2-(3-triethylsilyloxyprop-1-oxy)pyridine-5-carboxylate (1.53g, 4.5mmol) was dissolved in dry THF (50ml) under argon, then diisobutyl-aluminium hydride (1.0M, 5ml, 5mmol) was added slowly. After stirring 25 for 1/2h, more diisobutylaluminium hydride (5ml) was added, and stirring continued for a further 1h. Methanol (11ml) and saturated sodium sulphate (14ml) were added, and the mixture stirred for 15minutes. The salts were filtered off through celite, the filtrate dried and evaporated to give the hydroxymethyl compound as a colourless oil (1.36g, 100%). This 30 material was dissolved in dichloromethane (50ml), activated manganese dioxide (2.7g) added, and the mixture stirred for 16h. After filtering, the filtrate was evaporated to give a colourless oil. This residue was purified by column chromatography, eluting with 10% ethyl acetate in hexane, to give the title compound (0.958g, 72%); δ_H ($CDCl_3$) 0.54-0.66 (6H, m, 3xSiCH₂), 0.89-1.0 (9H, m, 3xCH₃), 2.02 (2H, q, J 6.2Hz, 2'-H₂), 3.80 (2H, t, J 6.2Hz, 3'-H₂), 4.51 (2H, t, J 6.3Hz, 1'-H₂), 6.82 (1H, d, J 8.8Hz, 3-H), 8.06 (1H, dd, J 8.7 and 2.4Hz, 4-H), 8.62 (1H, d, J 2.4Hz, 6-H), and 9.95 35 (1H, s, CHO); m/z (NH₃ DCI) 296 (MH^+ , 100%); m/z 296 (M^+ , 1%), 266

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(M-Et⁺, 68), 208 (100), and 124 (70). (Found: MH⁺, 296.1681. C₁₅H₂₆NO₃Si requires M, 296.1682. Found M-Et⁺, 266.1203. C₁₃H₂₀NO₃Si requires M, 266.1212).

- 5 d) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-(3-triethylsilyloxyprop-1-oxy)pyrid-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 10 2mmol) and 2-(3-triethylsilyloxyprop-1-oxy)pyridine-5-carboxaldehyde (0.650g, 2.2mmol) were reacted to give the title compound (1.454g, 89%); δ_H (CDCl₃) inter alia 0.54-0.65 (6H, m, 3xSiCH₂), 0.86-1.00 (12H, m, 4xCH₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 1.94-2.05 (2H, m, 2"-H₂), 4.12 (1H, dt, J 9.6 and 2.9Hz, 5-H), 4.38 (2H, t, J 6.2Hz, 1"-H₂), 5.09-5.18 (1H, m, 1-15 H), 6.73 (1H, d, J 8.5Hz, 3'-H), 7.60-7.68 (1H, m, 4'-H), and 8.11 (1H, d, J 2.2Hz, 6'-H); m/z 813 (M⁺, 0.4%), 266(56), 208(72), 117(61), and 73(100). (Found: M⁺, 813.4509. C₃₉H₇₅NO₉Si₄ requires M, 813.4519).

- e) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-(3-triethylsilyloxyprop-1-oxy)pyrid-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-(3-triethylsilyloxyprop-1-oxy)pyridine-5-carboxaldehyde (0.650g, 2.2mmol) were reacted to give the title compound (1.454g, 89%); δ_H (CDCl₃) inter alia 0.54-0.65 (6H, m, 3xSiCH₂), 0.86-1.00 (12H, m, 4xCH₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 1.94-2.05 (2H, m, 2"-H₂), 4.12 (1H, dt, J 9.6 and 2.9Hz, 5-H), 4.38 (2H, t, J 6.2Hz, 1"-H₂), 5.09-5.18 (1H, m, 1-H), 6.73 (1H, d, J 8.5Hz, 3'-H), 7.60-7.68 (1H, m, 4'-H), and 8.11 (1H, d, J 2.2Hz, 6'-H); m/z 813 (M⁺, 0.4%), 266(56), 208(72), 117(61), and 73(100). (Found: M⁺, 813.4509. C₃₉H₇₅NO₉Si₄ requires M, 813.4519).

- e) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-(3-triethylsilyloxyprop-1-oxy)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 49d (1.426g, 1.75mmol) in benzene (70ml) was reacted with manganese dioxide (3.5g)

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for 3h to give the title compound (0.770g, 54%); δ_H ($CDCl_3$) *inter alia* 0.55-0.66 (6H, m, 3xSiCH₂), 0.87-1.0 (12H, m, 4xCH₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 1.95-2.06 (2H, m, 2"-H₂), 4.46 (2H, t, J 6.3Hz, 1"-H₂), 6.19 (1H, s, 2-H), 6.77 (1H, d, J 8.8Hz, 3'-H), 8.06 (1H, dd, J 8.7 and 2.5Hz, 4'-H), and 8.70 (1H, d, J 2.3Hz, 6'-H); m/z 811 (M^+ , 0.1%), 782(2), 117(68), 5 and 73(100); m/z (NH₃ DCI) 812 (MH^+ , 1%), 191(25), 132(45), and 90(100). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

10 f) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-(3-hydroxyprop-1-oxy)pyrid-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 49e (0.740g, 0.91mmol) was completely deprotected to give the title compound (0.286g, 15 65%); ν_{max} (KBr) 3487, 1604, 1493, 1313, 1293, and 1058cm⁻¹; λ_{max} (EtOH) 319nm (ϵ_m 20,731); δ_H (CD_3OD) *inter alia* 0.94 (3H, d, J 7.2Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 1.91-2.08 (3H, m, 8-H, 2"-H₂), 3.73 (2H, t, J 6.3Hz, 3"-H₂), 4.46 (2H, t, J 6.3Hz, 1"-H₂), 6.36 (1H, s, 2-H), 6.86 (1H, d, J 8.8Hz, 3'-H), 8.17 (1H, dd, J 8.8 and 2.5Hz, 4'-H), and 8.72 (1H, 20 d, J 2.3Hz, 6'-H); δ_C (CD_3OD) 12.3 (C-17), 20.3 (C-14), 33.0 (C-9 and 2"), 41.7 (C-8), 42.5 (C-4), 43.7 (C-12), 56.7 (C-10), 59.5 (C-3"), 61.2 (C-11), 64.8 (C-1"), 66.4 (C-16), 69.8 (C-6), 70.7 (C-13), 71.5 (C-7), 75.5 (C-5), 97.7 (C-2), 112.0 (C-3'), 125.6 (C-5'), 138.7 (C-4'), 148.5 (C-6'), 167.8 (C-2'), 183.0 (C-1), and 194.9 (C-3); m/z 481 (M^+ , 0.5%), 138(60), and 122(100). (Found: 25 M^+ , 481.2313. $C_{24}H_{35}NO_9$ requires M , 481.2312). A further quantity of the title compound (0.122g, 28%) was obtained after chromatography of the mother liquors. The n.m.r. spectra indicated that the compound was essentially in the enolic form.

30 EXAMPLE 50

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxythiazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

35 a) 2-Methoxythiazole-5-carboxaldehyde

2-Methoxythiazole (contained 25% 2-bromothiazole, 0.50g, 4.3mmol) was dissolved in THF (20ml), cooled to -70%, and treated dropwise with n-

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butyllithium (1.5M, 3.2ml, 4.8mmol). The mixture was stirred for 75 minutes, then N,N-dimethylformamide (1.16ml, 15mmol) added. Stirred for a further 1 $\frac{1}{2}$ h, then quenched with saturated ammonium chloride and ether. The phases were separated, the organic washed with water, 5 dried and reduced to a small volume. The crude product was purified by flash chromatography, eluting with 50% ether in pentane, to give the title compound as an orange oil (1.08g); δ_H (CDCl₃) 4.18 (3H, s, OCH₃), 7.86 (1H, s, 4-H), and 9.83 (1H, s, CHO), signals were also observed for solvents and a few minor impurities.

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b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-methoxythiazol-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

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Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and the product from 50a (max. 3.2mmol) were reacted to give the title compound (1.032g, 78%); δ_H (CDCl₃) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.05 (3H, s, OCH₃), 5.21-5.32 (1H, m, 1-H), and 6.98 (1H, s, 4'-H); m/z 661 (M⁺, 1%), 226 (20), 143 (39), 129 (46), 117 (72), and 73 (100). (Found: M⁺, 661.2968. C₂₉H₅₅NO₈SSi₃ requires M, 661.2956).

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c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-methoxythiazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

25

Using the method described in 6b, the product from 50b (1.000g, 1.51mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 3h to give the title compound (0.431g, 43%); δ_H (CDCl₃) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.13 (3H, s, OCH₃), 5.96 (1H, s, 2-H), and 7.75 (1H, s, 4'-H); m/z 659 (M⁺, 0.1%), 644 (0.2), 184(29), 142(40), 117(89), and 73(100); m/z (NH₃ DCI) 660 (MH⁺, 22%) and 90(100).. The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

30

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxythiazol-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

35

Using the method described in 5c, the product from 50c (0.415g, 0.63mmol) was deprotected to give the title compound (0.243g, 87%); ν_{max} (KBr) 3424, 1616, 1488, 1401, 1277, 1109, and 1048cm⁻¹; λ_{max} (EtOH) 5 325nm (ϵ_m 15,668); δ_H (CD₃OD) 0.94 (3H, d, J 7.2Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 4.13 (3H, s, OCH₃), 6.17 (1H, s, 2-H), and 7.93 (1H, s, 4'-H); δ_C (CD₃OD) 12.3 (C-17), 20.3 (C-14), 33.0 (C-9), 40.3 (C-4), 41.8 (C-8), 43.8 (C-12), 56.9 (C-10), 59.9 (OCH₃), 61.3 (C-11), 66.4 (C-16), 69.8 (C-6), 10 70.7 (C-13), 71.6 (C-7), 75.5 (C-5), 97.9 (C-2), 132.0 (C-5'), 143.3 (C-4'), 160.9 (C-2'), 183.9 (C-1), and 188.1 (C-3); m/z (NH₃ DCI) 444 (MH^+ , 100%), 158(33), 91(79), and 74(38); m/z 443 (M^+ , 0.5%), 157(51), and 142(100). (Found: M^+ , 443.1665. C₂₀H₂₉NO₈S requires M , 433.1614). The n.m.r. spectra indicated that the title compound was mainly in the enolic form.

15

EXAMPLE 51

3R,4R-Dihydroxy-2S-[4-(cyclohexen-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

20

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-(cyclohexen-1-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

25

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and cyclohexene-1-carboxaldehyde (2.2mmol) were reacted to give the title compound (0.593g, 47%); δ_H (CDCl₃) inter alia 0.89 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 4.13 (1H, td, J 9.5 and 3.0Hz, 5-H), 4.37-4.48 (1H, m, 1-H), and 5.72 (1H, br s, 2'-H); m/z (NH₃ DCI) 646 (MNH⁺, 15%), 629 (MH^+ , 3), 536(50), 519 (18), 128(100), and 90(83).

b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(cyclohexen-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

35

Using the method described in 6b, the product from 51a (0.58g, 0.92mmol) in benzene (70ml) was reacted with manganese dioxide (1.8g) for 3¹/₂h to give the title compound (0.224g, 39%); δ_H (CDCl₃) inter alia 0.89 (3H, d, J

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7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 5.76 (1H, s, 2-H), and 6.90 (1H, br s, 2'-H); m/z 626 (M^+ , 2%), 611 (0.5), 334 (13), 151 (33), 117 (72), and 73 (100). (Found: M^+ , 626.3492. C₃₁H₅₈O₇Si₃ requires M , 626.3491). The ¹H n.m.r. spectrum indicated that the title compound was
5 essentially in the enolic form.

c) 3R,4R-Dihydroxy-2S-[4-(cyclohexen-1-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

10 Using the method described in 5c, the product from 51b (0.212g, 0.34mmol) was deprotected to give the title compound (0.134g, 97%); ν_{max} (KBr) 3423, 2927, 1640, 1588, 1450, 1110, and 1080cm⁻¹; λ_{max} (EtOH) 307nm (ϵ_m 12,570); δ_H (CD₃OD) *inter alia* 0.94 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.5Hz, 14-H₃), 1.56-1.78 (6H, m, 9-H₂, 4'-H₂, 5'-H₂), 2.14-15 2.33 (4H, m, 3'-H₂, 6'-H₂), 5.86 (1H, s, 2-H), and 6.92 (1H, br s, 2'-H); δ_C (CD₃OD) 12.3 (C-17), 20.3 (C-14), 22.7, 23.2, 24.5 and 27.0 (C-3', 4', 5' and 6'), 33.0 (C-9), 41.7 (C-8), 43.3 (C-4), 43.7 (C-12), 56.9 (C-10), 61.2 (C-11), 66.4 (C-16), 69.8 (C-6), 70.7 (C-13), 71.5 (C-7), 75.4 (C-5), 97.3 (C-2), 134.8 (C-1'), 137.7 (C-2'), 182.9 (C-1), 199.2 (C-3); m/z 410 (M^+ , 2%), 151 (52), 20 and 109 (100). (Found: M^+ , 410.2307. C₂₂H₃₄O₇ requires M , 410.2305).
The n.m.r. spectra indicated that the title compound was essentially in the enolic form.

25 EXAMPLE 52

3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(furan-2-yl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

30 a) 3R,4R-Bistrimethylsilyloxy-2S-[1-(furan-2-yl)-3-hydroxy-5-oxohex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 35 2mmol) and 3-(furan-2-yl)propenal (0.269g, 2.2mmol) were reacted to give the title compound (1.207g, 94%); δ_H (CDCl₃) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 4.7-4.8 (1H, m, 1-H), 6.14

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(1H, dd, J 15.8 and 5.4Hz, 1'-H), 6.23 (1H, d, J 3.3Hz, 3"-H), 6.36 (1H, dd, J 3.3 and 1.8Hz, 4"-H), 6.49 (1H, dd, J 15.8 and 1.0Hz, 2'-H), and 7.34 (1H, d, J 1.4Hz, 5"-H); m/z 640 (M^+ , 0.4%), 622 (0.4), 129 (54), 117 (100), and 73 (98). (Found: M^+ , 640.3267. $C_{31}H_{56}O_8Si_3$ requires M , 640.3283).

5

b) 3R,4R-Bistrimethylsilyloxy-2S-[3,5-dioxo-1-(furan-2-yl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

10 Using the method described in 6b, the product from 52a (1.187g, 1.85mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 2h to give the title compound (0.820g, 69%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 5.71 (1H, s, 2-H), 6.38 (1H, d, J 15.6Hz, 1'-H), 6.47 (1H, dd, J 3.4 and 1.9Hz, 4"-H), 6.57 (1H, 15 d, J 3.4Hz, 3"-H), 7.34 (1H, d, J 15.6Hz, 2'-H), and 7.48 (1H, d, J 1.5Hz, 5"-H); m/z 638 (M^+ , 1%), 623(1), 121(67), 117(89), and 73(100). (Found: M^+ , 638.3140. $C_{31}H_{54}O_8Si_3$ requires M , 638.3127). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

20 c) 3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(furan-2-yl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 52b (0.781g, 1.22mmol) was deprotected to give the title compound (0.477g, 93%); m.p. 25 150-151°C; ν_{max} (KBr) 1632, 1594, 1458, 1115, 1017, and 756cm⁻¹; λ_{max} (EtOH) 358nm (ϵ_m 33,626); δ_H (CD_3OD) *inter alia* 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 5.82 (1H, s, 2-H), 6.43 (1H, d, J 15.7Hz, 1'-H), 6.54 (1H, dd, J 3.4 and 1.9Hz, 4"-H), 6.71 (1H, d, J 3.4Hz, 3"-H), 7.36 (1H, d, J 15.7Hz, 2'-H), and 7.62 (1H, d, J 1.4Hz, 5"-H); δ_c (30 CD_3OD) 12.2 (C-17), 20.3 (C-14), 33.0 (C-9), 41.7 (C-8), 43.7 (C-12), 44.1 (C-4), 56.8 (C-10), 61.3 (C-11), 66.4 (C-16), 69.8 (C-6), 70.7 (C-13), 71.5 (C-7), 75.3 (C-5), 102.5 (C-2), 113.5, 115.4, 121.3, 127.2, and 146.2 (C-1', 2', 3", 4" and 5"), 153.1 (C-2") (C-3 and 1 not visible); m/z 422 (M^+ , 4%), 163 (40), and 121(100). (Found: M^+ , 422.1946. $C_{22}H_{30}O_8$ requires M , 422.1941). The spectra indicated that the title compound was essentially in the enolic form.

EXAMPLE 53

3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(4-methoxyphenyl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

- 5 a) 3R,4R-Bistrimethylsilyloxy-2S-[3-hydroxy-1-(4-methoxyphenyl)-5-oxohex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 10 2mmol) and 4-methoxycinnamaldehyde (0.357g, 2.2mmol) were reacted to give the title compound (1.200g, 88%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 3.81 (3H, s, OCH₃), 4.68-4.78 (1H, m, 1-H), 6.07 (1H, dd, J 15.9 and 6.1Hz, 1'-H), 6.58 (1H, d, J 15.9Hz, 2'-H), 6.85 (2H, d, J 8.7Hz, 2"-H, 6"-H), and 7.31 (2H, d, J 8.7Hz, 3"-H, 5"-H); m/z (NH₃ DCI) 698 (MNH_4^+ , 5%), 680 (MH^+ , 1), 180(38), 163(100), 15 and 90(52).

- b) 3R,4R-Bistrimethylsilyloxy-2S-[3,5-dioxo-1-(4-methoxyphenyl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 53a (1.157g, 1.70mmol) in benzene (70ml) was reacted with manganese dioxide (3.0g) for 2h to give the title compound (0.840g, 73%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.84 (3H, s, OCH₃), 5.71 (1H, s, 2-H), 6.36 (1H, d, J 15.9Hz, 1'-H), 6.90 (2H, d, J 8.8Hz, 2"-H, 6"-H), 7.47 (2H, d, J 8.8Hz, 3"-H, 5"-H), and 7.56 (1H, d, J 15.9Hz, 2'-H); m/z 678 (M^+ , 0.4%), 663 (0.7), 161(82), 117(63), and 73(100). (Found: M^+ , 678.3451. C₃₄H₅₈O₈Si₃ requires M , 678.3440). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

- c) 3R,4R-Dihydroxy-2S-[3,5-dioxo-1-(4-methoxyphenyl)hex-1(E)-en-6-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

35 Using the method described in 5c, the product from 51b (0.815g, 1.2mmol) was deprotected to give the title compound (0.468g, 84%); m.p. 130-132°C; ν_{max} (KBr) 3495, 1636, 1588, 1511, 1251, 1174, and 1114cm⁻¹; λ_{max} (EtOH) 359nm (ϵ_m 35,962); δ_H (CD_3OD) *inter alia* 0.94 (3H, d, J 7.0Hz,

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17-H₃), 1.19 (3H, d, J 6.5Hz, 14-H₃), 3.82 (3H, s, OCH₃), 5.82 (1H, s, 2-H),
6.51 (1H, d, J 15.9Hz, 1'-H), 6.95 (2H, d, J 8.8Hz, 2"-H, 6"-H), and 7.54
(3H, 2d, J 15.9 and 8.8Hz, 2'-H, 3"-H, 5"-H); δ_{C} (CD₃OD/CDCl₃) 12.2 (C-
17), 20.3 (C-14), 32.6 (C-9), 41.1 (C-8), 43.3 (C-12), 43.7 (C-4), 55.8
5 (OCH₃), 56.6 (C-10), 61.1 (C-11), 66.2 (C-16), 69.4 (C-6), 70.5 (C-13), 71.1
(C-7), 75.0 (C-5), 101.8 (C-2), 115.1 (C-2" and 6"), 121.0 (C-2'), 128.7 (C-1"),
130.4 (C-3" and 5"), 140.6 (C-1'), 162.3 (C-4"), 178.1 (C-1), and 199.4 (C-3);
m/z 462 (M⁺, 0.6%) and 161(100). (Found: M⁺, 462.2270. C₂₅H₃₄O₈
requires M, 462.2254). The n.m.r. spectra indicated that the title
10 compound was essentially in the enolic form.

EXAMPLE 54

15 3R,4R-Dihydroxy-2S-(3,5-dioxo-1-phenylhex-1-yn-6-yl)-5S-(2S,3S-epoxy-
5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-(3-hydroxy-5-oxo-1-phenylhex-1-yn-
6-yl)-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-
methylhexyl)tetrahydropyran

20 Using the method described in 5a, tristrimethylsilylmonone (1.038g,
2mmol) and phenylpropynal (0.27ml, 2.2mmol) were reacted to give the
title compound (1.139g, 86%); δ_{H} (CDCl₃) inter alia 0.90 (3H, d, J 7.0Hz,
17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 5.00-5.10 (1H, m, 1-H), and 7.27-7.49
25 (5H, m, Ar-H); m/z 648 (M⁺, 6%), 117(80), and 73(100). (Found: M⁺,
648.3346. C₃₃H₅₆O₇Si₃ requires M, 648.334).

b) 3R,4R-Bistrimethylsilyloxy-2S-(3,5-dioxo-1-phenylhex-1-yn-6-yl)-
5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

30 The product from 52a (0.660g, 1mmol) in dichloromethane (60ml) was
stirred with manganese dioxide (active black, 1.38g) at room temperature
for 75 minutes. After this time the mixture was filtered and the filtrate
evaporated. The crude product was purified by column chromatography,
35 eluting with 8-10% ethyl acetate in hexane, to give the title compound
(0.328g, 50%); δ_{H} (CDCl₃) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20
(3H, d, J 6.3Hz, 14-H₃), 5.95 (1H, s, 2-H), and 7.32-7.60 (5H, m, Ar-H);
m/z 646 (M⁺, 0.2%), 631 (0.6), 258(28), 186(41), 117(46), and 73(100).

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(Found: M^+ , 646.3164. $C_{33}H_{54}O_7Si_3$ requires M , 646.3177). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

5 c) 3R,4R-Dihydroxy-2S-(3,5-dioxo-1-phenyl(hex-1-yn-6-yl))-5S-(2S,3S-
epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 54b (0.320g, 0.49mmol) was deprotected to give the title compound (0.117mg, 55%);
10 ν_{max} (KBr) 3419, 2203, 1602, 1443, 1110, 1043, and 758cm⁻¹; λ_{max} (EtOH) 328nm (ϵ_m 20,521); δ_H (CD₃OD) *inter alia* 0.94 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 5.98 (1H, s, 2-H, exchanging rapidly), and 7.38-7.61 (5H, m, Ar-H); δ_C (CDCl₃) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 36.4 (C-4), 39.7 (C-8), 42.8 (C-12), 55.7 (C-10), 61.3 (C-11), 65.7 (C-16), 68.7 (C-6), 70.1 (C-7), 71.2 (C-13), 73.7 (C-5), 85.1 and 94.3 (C=C), 105.6 (C-2), 120.3 (C-1'), 126.0-132.6 (C-Ar), C-1 and C-3 assignments uncertain as all forms rapidly interconverting; m/z 430 (M^+ , 18%), 412(5), 200(30), 186(100), and 110(66). (Found: M^+ , 430.1984. $C_{24}H_{30}O_7$ requires M , 430.1992). The spectra indicated that the title compound was mainly in the enolic form.

EXAMPLE 55

25 3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrimidin-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 2-Dimethylaminopyrimidine-5-carboxaldehyde

5-Bromo-2-chloropyrimidine was converted, using the methods described in 30a, to the title compound (0.495g, 52%); δ_H (CDCl₃) 3.31 (6H, s, N(CH₃)₂), 8.73 (2H, s, 4-H, 6-H), and 9.77 (1H, s, CHO); m/z 151 (M^+ , 100%), 136(55), 122(74), and 95(45). (Found: M^+ , 151.0747. $C_9H_9N_3O$ requires M , 151.0746).

35 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-dimethylaminopyrimidin-5-yl)-4-hydroxy-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

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Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and 2-dimethylaminopyrimidine-5-carboxaldehyde (0.333g, 2.2mmol) were reacted to give the title compound (0.997g, 74%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 3.20 (6H, s, $N(CH_3)_2$), 4.95-5.05 (1H, m, 1-H), and 8.33 (2H, s, 4'-H, 6'-H); m/z 669 (M⁺, 1%), 176(48), 151(42), 129(72), 117(93), and 73(100). (Found: M⁺, 669.3645. $C_{31}H_{59}N_3O_7Si_3$ requires M, 669.3661).

10 c) 3R,4R-Bistrimethylsilyloxy-2S-[4-(2-dimethylaminopyrimidine-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

15 Using the method described in 6b, the product from 53b (0.949g, 1.42mmol) in benzene (70ml) was reacted with manganese dioxide (3g) for 3h to give the title compound (0.421g, 45%); δ_H ($CDCl_3$) inter alia 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 3.28 (6H, s, $N(CH_3)_2$), 6.07 (1H, s, 2-H), and 8.80 (2H, s, 4'-H, 6'-H); m/z 667 (M⁺, 1%), 652(2), 192(50), 150(74), and 73(100). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

20 d) 3R,4R-Dihydroxy-2S-[4-(2-dimethylaminopyrimidin-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

25 Using the method described in 5c, the product from 53c (0.387g, 0.58mmol) was deprotected to give the title compound (0.253g, 97%); ν_{max} (KBr) 3478, 1604, 1559, 1412, 1326, 1284, 1109, and 1059cm⁻¹; λ_{max} (EtOH) 344nm (ϵ_m 29,858); δ_H (CD_3OD) inter alia 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.4Hz, 14-H₃), 3.26 (6H, s, $N(CH_3)_2$), 6.26 (1H, s, 2-H), and 8.81 (2H, s, 4'-H, 6'-H); δ_C ($CD_3OD/CDCl_3$) 12.2 (C-17), 20.2 (C-14), 32.6 (C-9), 37.6 ($N(CH_3)_2$), 41.2 (C-8), 41.6 (C-4), 43.3 (C-12), 56.6 (C-10), 61.1 (C-11), 66.2 (C-16), 69.4 (C-6), 70.5 (C-13), 71.1 (C-7), 75.1 (C-5), 96 (C-2), 117.3 (C-5'), 158.4 (C-4' and 6'), 163.4 (C-2'), 183.1 (C-1), and 191.6 (C-3); m/z 451 (M⁺, 2%), 166(30), and 150(100). (Found: M⁺, 451.2343. $C_{22}H_{33}N_3O_7$ requires M, 451.2319). The n.m.r. spectra indicated that the title compound was essentially in the enolic form.

EXAMPLE 56

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

5 a) 2-Methoxypyrimidine-5-carboxaldehyde

Using the method described in 21a, 5-bromo-2-methyoxyprymidine (0.58g, 3.07mmol) was converted to the title compound (0.185g, 44%); δ_H ($CDCl_3$) 4.14 (3H, s, OCH₃), 9.00 (2H, s, 4-H, 6-H), and 10.03 (1H, s, CHO); m/z 138 (M^+ , 100%), 123(20), and 108(80). (Found: M^+ , 138.0433. C₆H₆N₂O₂ requires M , 138.0429).

10 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-4-(2-methoxypyrimidin-5-yl)-2-oxobut-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

15 Using the method described in 5a, tristrimethylsilylmonone (0.50g, 0.97mmol) and 2-methoxypyrimidine-5-carboxaldehyde (0.134g, 0.97mmol) were reacted to give the title compound (0.384g, 61%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.4Hz, 14-H₃), 4.02 (3H, s, OCH₃), 5.11-5.21 (1H, m, 1-H), and 8.53 (2H, s, 4'-H, 6'-H); m/z (NH₃ DCI) 657 (MH^+ , 70%), 536(31), and 139(100).

20 c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(2-methoxypyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

25 Using the method described in 6b, the product from 54b (0.373g, 0.57mmol) in benzene (50ml) was reacted with manganese dioxide (1.0g) for 3h to give the title compound (0.160g, 43%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.3Hz, 14-H₃), 4.09 (3H, s, OCH₃), 6.17 (1H, s, 2-H), and 8.98 (2H, s, 4'-H, 6'-H); m/z 654 (M^+ , 2%), 639(1), 117(98), and 73(100). (Found: M^+ , 654.3186. C₃₀H₅₄N₂O₈Si₃ requires M , 654.3188).

30 35

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrimidin-5-yl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

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Using the method described in 5c, the product from 54c (0.15g, 0.23mmol) was deprotected to give the title compound (0.045g, 45%); δ_H (CD_3OD) 0.94 (3H, d, J 7.0Hz, 17-H₃), 1.19 (3H, d, J 6.5Hz, 14-H₃), 1.30-1.48 (1H, m, 12-H), 1.64-1.74 (2H, m, 9-H₂), 1.91-2.03 (1H, m, 8-H), 2.52 (1H, dd, J 14.8 and 9.4Hz, 4-H), 2.70 (1H, dd, J 7.5 and 2.2Hz, 11-H), 2.81 (1H, dt, J 5.7 and 2.2Hz, 10-H), 2.92 (1H, dd, J 14.8 and 2.9Hz, 4-H), 3.44 (1H, dd, J 9.2 and 3.0Hz, 6-H), 3.57 (1H, d, J 11.3Hz, 16-H), 3.73-3.84 (1H, m, 13-H), 3.87-3.95 (2H, m, 7-H, 16-H), 4.03 (1H, dt, J 3.0 and 9.4Hz, 5-H), 4.09 (3H, s, OCH_3), 6.42 (1H, s, 2-H), and 9.08 (2H, s, 4'-H, 6'-H); m/z 438 (M^+ , 3%), 153(71), and 137(100). (Found: M^+ , 438.2007. $C_{21}H_{30}N_2O_8$ requires M , 438.2002). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 57

15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-
(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

20 a) 4-(2-Azidoethoxy)benzaldehyde

25 A solution of 4-(2-hydroxyethoxy)benzaldehyde (1.328g, 8mmol) in dichloromethane (30ml) was treated with triethylamine (1.34mmol, 9.6mmol) and methane sulphonyl chloride (0.7ml, 9mmol). After 1 hour the reaction mixture was diluted with dichloromethane, washed with dilute citric acid, saturated sodium hydrogen carbonate and brine then dried and evaporated.

30 The residue was dissolved in dichloromethane (30ml) and treated with tetramethyl guanidinium azide (1.42g, 9mmol). After 24 hours more tetramethyl guanidinium azide (1.42g, 9mmol) was added and the mixture was heated at 40°C. After 48 hours at 40°C followed by 2 days at room temperature the reaction mixture was washed with water, dilute citric acid, saturated sodium hydrogen carbonate and brine then dried and evaporated. Chromatography on silica eluting with ethyl acetate hexane mixtures gave the title compound (1.17g, 76%); ν_{max} (CH_2Cl_2) 2105, 1675, 1600cm⁻¹; δ_H ($CDCl_3$) 3.65 (2H, t, J 5.0Hz), 4.24 (2H, t, J 5.0Hz), 7.06 (2H, d, J 8.8Hz), 7.88 (2H, d, J 8.8Hz), 9.91 (1H, s).

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b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

5 Using the method described in 5a, tristrimethylsilylmonone (2.076g, 4mmol) and the product from 57a (764mg, 4mmol) were reacted to give the title compound (2.31g, 81%); δ_H ($CDCl_3$) *inter alia* 0.88 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.59 (2H, t, J 5.0Hz, ArOCH₂), 5.06-5.18 (1H, m, 1-H), 6.90 (2H, d, J 8.6Hz, 3',5'-H₂), 7.25-7.38 (2H, m, 2',6'-H₂).

c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

15 Using the method described in 6b, the product from 57b (2.25g, 3.17mmol) in benzene (140ml) was reacted with manganese dioxide (4.51g), for 3 hours to give the title compound (1.35g, 60%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.63 (2H, t, J 5.0Hz, 1"-H₂), 4.22 (2H, t, J 5.0Hz, 2"-H₂), 6.22 (1H, s, 2-H), 6.96 (2H, d, J 8.8Hz, 3',5'-H₂), 7.88 (2H, d, J 8.8Hz, 2',6'-H₂); (Found M^+ , 707.3439. $C_{33}H_{57}N_3O_8Si_3$ requires M 707.3454).

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-2-oxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 57c (120mg, 0.17mmol) was deprotected to give the title compound (70mg, 90%); ν_{max} (KBr) 3424, 2112, 1604, 1507cm⁻¹; λ_{max} (EtOH) 324.5nm (ϵ_m 21,280); δ_H ($CDCl_3$) *inter alia* 0.94 (3H, d, J 7.1Hz, 17-H₃), 1.21 (3H, d, J 6.3Hz, 14-H₃), 4.21 (2H, t, J 5.2Hz, 2"-H₂), 6.21 (1H, s, 2-H), 6.98 (2H, d, J 8.9Hz, 3'5'-H₂), 7.86 (2H, d, J 8.9Hz, 2'6'-H₂); δ_C ($CDCl_3$) 12.7 (C-17), 20.8 (C-14), 31.6 (C-9), 39.6 (C-8), 42.8 (C-4), 42.8 (C-12), 50.0 (C-1"), 55.7 (C-10), 61.3 (C-11), 65.6 (C-16), 67.2 (C-2"), 69.0 (C-7), 70.3 (C-6), 171.3 (C-13), 73.9 (C-5), 96.7 (C-2), 114.5 (C-3',5'), 127.5 (C-1'), 129.3 (C-2'6'), 161.8 (C-4'), 182.7 (C-1), 194.3 (C-3); m/z (NH₃DCI) 492 (MH^+ , 100%). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 58

5 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-N-methyl-N-2-pyridylaminoethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-[2-N-methyl-N-2-pyridylaminoethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

10 Using the method described in 5a, tristrimethylsilylmonone (518mg, 1mmol) and 4-(2-N-methyl-N-2 pyridylaminoethoxy)benzaldehyde (256mg, 1mmol) were reacted to give the title compound (580mg, 75%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, 7.0Hz, 17-H₃), 1.20 (3H, d, 6.3Hz, 14-H₃), 3.15 (3H, s, N-Me), 5.06-5.16 (1H, m, 1-H), 6.48-6.59 (2H, m, Ar-H), 6.88 (2H, d, *J* 8.8Hz, 3',5'-H₂), 7.21-7.30 (2H, m, Ar-H), 7.41-7.52 (1H, m, Ar-H), 8.03-8.19 (1H, m, Ar-H); *m/z* (NH₂ DCI) 775 (MH^+ , 5%), 257 (100%).

b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-[2-N-methyl-N-2-pyridylaminoethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 6b, the product from 58a (560mg, 0.72mmol) in benzene (60ml) was reacted with manganese dioxide (1.12g) for 4 hours to give the title compound (277mg, 49%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, *J* 7.0Hz, 17-H₃), 1.20 (3H, d, *J* 6.3Hz, 14-H₃), 3.16 (3H, s, N-Me), 4.26 (2H, t, *J* 5.5Hz, 1'-H₂), 6.20 (1H, s, 2-H), 6.48-6.62 (2H, m, 3'',5''-H₂), 6.94 (2H, d, *J* 8.8Hz, 3',5'-H₂), 7.47 (1H, dd, *J* 1.9, 7.1Hz, 5'''-H), 7.84 (2H, d, *J* 8.8Hz, 3',6'-H₂), 8.18 (1H, dd, *J* 1.4, 4.8Hz, 6'''-H₂); (Found: M^+ , 772.3983. C₃₉H₆₄N₂O₈Si₃ requires M 772.3971).

c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-N-methyl-N-2-pyridylaminoethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

35 Using the method described in 5c, the product from 58b (250mg, 0.32mmol) was deprotected to give the title compound (180mg, 94%); ν_{max} (KBr) 3423, 1599, 1558, 1499, 1452cm⁻¹; λ_{max} (EtOH) 324.5nm (ϵ_m

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25,150), 248.5 (18,530); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 3.13 (3H, s, N-Me), 4.27 (2H, t, J 5.5Hz, 1"-H₂), 6.21 (1H, s, 2-H), 6.53 (1H, d, J 8.7Hz, 3'"-H), 6.58 (1H, dd, J 5.0, 6.8Hz, 5""-H), 6.95 (2H, d, J 8.8Hz, 3',5'-H₂), 7.48 (1H, dd, J 1.9, 7.1Hz, 4""-H), 7.86 (2H, d, J 8.8Hz, 3',6'-H₂), 8.17 (1H, d, J 4.9Hz, with further fine coupling, 6""-H); δ_C ($CDCl_3$) 12.7 (C-17), 20.7 (C-14), 31.6 (C-9), 37.8 (N-Me), 39.6 (C-8), 42.7 (C-4), 42.8 (C-12), 49.3 (C-1"), 55.7 (C-10), 61.2 (C-11), 65.6 (C-16), 66.7 (C-2"), 69.2 (C-7), 70.3 (C-6), 71.3 (C-13), 73.8 (C-5), 96.4 (C-2), 105.7 (C-2""), 111.9 (C-5""), 114.5 (C-3'5'), 126.7 (C-1'), 129.2 (C-2',6'), 137.3 (C-4""), 147.8 (C-6""), 158.2 (C-4'), 162.6 (C-2""), 182.8 (C-1), 193.9 (C-3); m/z (NH₃ DCI) 556 (M^+ , 55%), 121 (100%). The 1H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

15 Example 59

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[2-piperidinylethoxy]phenyl)but-1-yl-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

20 a) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-[2-piperidinylethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.0388g, 2mmol) and 4(2-piperidinylethoxy)benzaldehyde (466mg, 2mmol) (HD Cossey *et al*, JCS, 1963, 4322) were reacted to give the title compound (1.0g, 66%); δ_H ($CDCl_3$) *inter alia* 0.90 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 5.08-5.18 (1H, m, 5-H), 6.87 (2H, d, J 8.7Hz, 3',5'-H₂), 7.23-7.34 (2H, m, 2',6'-H₂).

30 b) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-[2-piperidinylethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

35 Using the method described in 6b, the product from 59a (1.0g, 1.3mmol) in benzene (70ml) was reacted with manganese dioxide (1.5g) for 3 hours to give the title compound (454mg, 45%); δ_H ($CDCl_3$) *inter alia* 0.89 (3H, d, J 7.0Hz, 17-H₃), 1.21 (3H, d, J 6.4Hz, 14-H₃), 6.20 (1H, s, 2-H), 6.93 (2H, d,

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J 8.8Hz, 3',5'-H₂), 7.87 (2H, d, J 8.8Hz, 2',6'-H₂); (Found: M⁺, 749.4181.
C₃₈H₆₇NO₈Si₃ requires M 749.4175).

- 5 c) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-piperidinylethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 59b (450mg, 0.6mmol) was deprotected to give the title compound (180mg, 56%); ν_{max} (KBr) 10 3425, 2933, 1602, 1509, 1453cm⁻¹; λ_{max} (EtOH) 326nm (ϵ_m 2000); δ_{H} (CDCl₃) *inter alia* 0.93 (3H, d, J 7.1Hz, 17-H₃), 1.22 (3H, d, J 6.3Hz, 14-H₃), 6.20 (1H, s, 2-H), 6.96 (2H, d, J 8.8Hz, 3',5'-H₂), 7.85 (2H, d, J 8.8Hz, 2',6'-H₂); δ_{C} (CDCl₃) 12.8 (C-17), 20.9 (C-14), 24.2 (C-4''), 25.9 (C-3'',5''), 31.8 (C-9), 42.7 (C-4), 43.0 (C-12), 55.2 (C-2'',6''), 55.8 (C-10), 57.8 (C-2''), 15 61.3 (C-11), 65.7 (C-16), 66.3 (C-1''), 69.2 (C-7), 70.5 (C-6), 71.9 (C-13), 74.0 (C-5), 96.6 (C-2), 114.7 (C-3',5'), 127.0 (C-1'), 129.3 (C-2'6'), 162.7 (C-4'), 183.0 (C-1), 194.0 (C-3); (Found: M⁺, 533.3001. C₂₉H₄₃NO₈ requires M 533.2989). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

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Example 60

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-(4-pyridylmethoxy)phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

25

- a) 4-(4-Pyridylmethoxy)benzaldehyde

A solution of *p*-hydroxybenzaldehyde (436mg, 4mmol) in THF (50ml) and 30 0°C under argon was sequentially treated with triphenylphosphine (2.1g, 8mmol), 4-hydroxymethylpyridine (976mg, 8mmol) and diethylazodicarboxylate (1.26ml, 8mmol). After $\frac{1}{4}$ hour ice bath removed. After 1 hour reaction mixture evaporated, added ethyl acetate and 5N hydrochloric acid. Acid phase separated, covered with ethyl acetate and basified with saturated sodium hydrogen carbonate. Organic phase 35 separated, dried and evaporated. The residue was chromatographed on silica eluting dichloromethane/ethyl acetate mixtures to give the title compound (440mg, 52%); δ_{H} (CD₃OD) 5.21 (2H, s, 1'-H₂), 7.04 (2H, d, J 8.7Hz, 3,5-H₂), 7.51 (2H, d, J 6.1Hz, 3',5'-H₂), 7.89 (2H, d, J 8.7Hz, 2,6-

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H₂), 8.60 (2H, d, J 6.1Hz, 2',6'-H₂), 9.92 (1H, s, -CHO).

- 5 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-pyridylmethoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and the product from 60a (426mg, 2mmol) were reacted to give the title compound (1.07g, 73%); δ_H (CDCl₃) *inter alia* 0.92 (3H, d, J 7.1Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 4.06-4.18 (1H, m, 5-H), 5.10 (2H, s, 1"-H₂), 5.10-5.18 (1H, m, 1-H), 6.93 (2H, d, J 8.7Hz, 3',5'-H₂), 7.23-7.39 (4H, m, Ar-H), 8.62 (2H, d, J 5.9Hz, 2'",6"-H₂); m/z (NH₃ DCI) 732 (MH⁺, 80%) 94 (100%).

- 15 c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-pyridylmethoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 6b, the product from 60b (1.0g, 1.37mmol) in benzene (70ml) was reacted with manganese dioxide (2.25g) for 3 hours to give the title compound (600mg, 60%); δ_H (CDCl₃) 0.90 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 5.16 (2H, s, 1"-H₂), 6.22 (1H, s, 2-H), 7.02 (2H, d, J 8.8Hz, 3',5'-H₂), 7.37 (2H, d, J 5.8Hz, 3'",5""-H₂), 7.89 (2H, d, J 8.8Hz, 2',6'-H₂), 8.65 (2H, d, J 5.8Hz, 2'",6""-H₂); (Found: 25 M⁺, 729.3545. C₃₇H₅₉NO₈Si₀3 requires M 729.3549.

- d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-pyridylmethoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

30 Using the method described in 5c, the product from 60c (40mg, 0.055mmol) was deprotected to give the title compound (22mg, 78%); ν_{max} (KBr) 3418, 1715, 1602, 1507, 1450cm⁻¹; λ_{max} (EtOH) 325nm (ϵ_m 21140); δ_H (CDCl₃) *inter alia* 0.92 (3H, d, J 7.0Hz, 17-H₃), 1.23 (3H, d, J 6.3Hz, 14-H₃), 5.15 (2H, s, 1"-H₂), 6.20 (2H, s, 2-H), 7.00 (2H, d, J 8.8Hz, 3',5'-H₂), 7.37 (2H, d, J 5.8Hz, 3'",5""-H₂), 7.88 (2H, d, J 8.8Hz, 2',6'-H₂), 8.63 (2H, d, J 5.8Hz, 2'",5"-H₂); m/z (NH₃ DCI) 514 (MH⁺, 55%), 94 (100%). The ¹H n.m.r. spectrum indicated that the title compound was essentially

in the enolic form.

Example 61

5 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{5-nitrofuran-2-ylmethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

a) 4-(5-Nitrofuran-2-ylmethoxy)benzaldehyde

10 A solution of 2-hydroxymethyl-5-nitrofuran (S. Brokerman and T. Globerman, Tet, 1974, 30, 3873) (1.22g, 10mmol) in THF (100ml) under argon at 5°C was sequentially treated with triphenylphosphine (2.62g, 10mmol), *p*-hydroxybenzaldehyde (1.14g, 8mmol) and dimethylazodicarboxylate (1.46g, 10mmol). After 2 hours reaction mixture diluted with ethyl acetate, washed with water then dried and evaporated. The residue was chromatographed on silica eluting with hexane/dichloromethane mixtures to give the title compound (1.6g, 81%); δ_H (CDCl₃) 5.19 (2H, s, 1'-H₂), 6.68 (1H, d, *J* 3.7Hz, 3"-H), 7.08 (2H, d, *J* 8.7Hz, 3,5-H₂), 7.34 (1H, d, *J* 3.7Hz, 4"-H), 7.90 (2H, d, *J* 8.7Hz, 2,6-H₂).

20 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-{5-nitrofuran-2-ylmethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

25 Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and the product from 61a (494mg, 2mmol) were reacted to give the title compound (1.16g, 76%); δ_H (CDCl₃) *inter alia* 0.90 (3H, d, *J* 7.1Hz, 17-H₃), 1.20 (3H, d, *J* 6.3Hz, 14-H₃), 5.06 (2H, s, 1"-H₂), 5.07-5.12 (1H, m, 1-H), 6.62 (1H, d, *J* 3.8Hz, 3'''-H), 6.92 (2H, d, *J* 8.7Hz, 3',5'-H₂), 7.26-7.48 (3H, m).

30 c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-{5-nitrofuran-2-ylmethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

35 Using the method described in 6b, the product from 61b (1.16g, 1.52mmol) in benzene (60ml) was reacted with manganese dioxide (3.02g) for 5 hours to give the title compound (270mg, 23%); δ_H (CDCl₃) *inter alia* 0.89 (3H,

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d, J 7.0Hz, 17-H₃), 1.18 (3H, d, J 6.4Hz, 14-H₃), 5.13 (2H, s, 1"-H₂), 6.20 (1H, s, 2-H), 6.63 (1H, d, J 3.6Hz, 3""-H), 6.96 (2H, d, J 9.0Hz, 3,5-H₂), 7.32 (1H, d, J 3.6Hz, 4""-H), 7.90 (2H, d, J 8.9Hz, 2',6'-H₂); m/z (NH₃ DCI) 781 (MNH_4^+ , 20%), 764 (MH^+ , 50%), 112 (100%).

5

d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[5-nitrofuran-2-ylmethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

10 Using the method described in 5c, the product from 61c (250mg, 0.33mmol) was deprotected to give the title compound (126mg, 70%); ν_{max} (KBr) 3463, 1604, 1507, 1468cm⁻¹; λ_{max} (EtOH) 319.5nm (ϵ_m 30,504); δ_H (d₄-MeOH) *inter alia* 0.96 (3H, d, J 7.0Hz, 17-H₃), 1.20 (3H, d, J 6.3Hz, 14-H₃), 5.23 (2H, s, 1"-H₂), 6.36 (1H, s, 2-H), 6.85 (1H, d, J 3.6Hz, 3""-H), 7.11 (2H, d, J 8.8Hz, 3',5'-H₂), 7.44 (1H, d, J 3.6Hz, 4""-H), 7.93 (2H, d, J 8.8Hz, 2',6'-H₂); δ_C (CD₃OD) 12.4(C-17), 20.5 (C-14), 33.1 (C-9), 41.8 (C-8), 42.7 (C-4), 43.9 (C-12), 57.0 (C-10), 61.4 (C-11), 63.2 (C-16), 66.7 (C-2''), 70.0 (C-7), 70.9 (C-6), 71.1 (C-13), 75.7 (C-5), 97.7 (C-2), 113.4 (C-2'''), 114.3 (C-3'''), 116.0 (C-3',5'), 129.6 (C-1'), 130.4 (C-2',6'), 154.9 (C-1'''), 162.9 (C-4'), 184.1 (C-1), 195.1 (C-3); m/z (NH₃ DCI) 565 (MNH_4^+ , 8%), 548 (MH^+ , 20%), 112 (100%). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Example 62

25

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-[furan-2-ylmethoxy]phenyl)but-1-yl]-5S-(2S,3S-epoxy-6S-hydroxy-4S-methylhexyl)tetrahydropyran

30

a) 4-(Furan-2-ylmethoxy)benzaldehyde
Furfurylalcohol (0.86ml, 10mmol) was added dropwise to a cold (5°C) mixture of sodium hydride (80%, 300mg, 10mmol) in DMF (40ml). After 1 hour *p*-fluoro-benzaldehyde (1.07ml, 10mmol) was added. After 3 hours reaction mixture poured into water and extracted with ethyl acetate.

35

Organic phase washed with dilute sodium carbonate and brine then dried and evaporated. Chromatography on silica eluting ethyl acetate/hexane mixtures gave the title compound (700mg, 35%); δ_H (CDCl₃) *inter alia* 5.10 (2H, s, 1'-H₂), 6.38 (1H, dd, J 1.9, 3.2Hz, 4"-H), 6.46 (1H, d, J 3.1Hz,

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5"-H), 7.04 (2H, d, *J* 8.7Hz, 3,5-H₂), 7.41 (1H, bs, 3"-H), 7.86 (2H, d, *J* 8.7Hz, 2,6-H₂), 9.92 (1H, s, CHO).

- 5 b) 3R,4R-Bistrimethylsilyloxy-2S-[4-hydroxy-2-oxo-4-(4-{furan-2-ylmethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5a, tristrimethylsilylmonone (1.038g, 2mmol) and the product from 62a (400mg, 2mmol) were reacted to give the title compound (686mg, 43%); δ_H (CDCl₃) *inter alia* 0.90 (3H, d, *J* 7.1Hz, 17-H₃), 1.21 (3H, d, *J* 6.3Hz, 14-H₃), 4.98 (2H, s, 1"-H₂), 5.06-5.17 (1H, m, 5-H), 6.39 (1H, dd, *J* 1.9, 3.2Hz, 4""-H), 6.41 (1H, d, *J* 3.2Hz, 3""-H), 6.96 (2H, d, *J* 8.6Hz, 3',5'-H₂), 7.24-7.35 (2H, m, 2',6'-H₂), 7.45 (1H, d, *J* 1.7Hz, 5'''-H); *m/z* (NH₃ DCI) 738 (MNH₄⁺, 25%), 203 (100%).

- 15 c) 3R,4R-Bistrimethylsilyloxy-2S-[2,4-dioxo-4-(4-{furan-2-ylmethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-trimethylsilyloxy-4S-methylhexyl)tetrahydropyran

20 Using the method described in 6b, the product from 62b (650mg, 0.9mmol) in benzene (60ml) was reacted with manganese dioxide (1.3g) for 3 hours to give the title compound (293mg, 43%); δ_H (CDCl₃) 0.89 (3H, d, *J* 7.1Hz, 17-H₃), 1.20 (3H, d, *J* 6.2Hz, 14-H₃), 4.07-4.18 (1H, m, 5-H), 5.07 (2H, s, 1"-H), 6.20 (1H, s, 2-H), 6.41 (1H, dd, *J* 1.9, 3.2Hz, 4""-H), 6.47 (1H, d, *J* 3.4Hz, 3""-H), 7.02 (2H, d, *J* 8.9Hz, 3',5'-H₂), 7.45 (1H, d, *J* 2.0Hz, 5'''-H), 7.88 (2H, d, *J* 8.9Hz, 3',6'-H₂); *m/z* (NH₃ DCI) 719 (MH⁺, 40%), 90 (100%).

- 30 d) 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{furan-2-ylmethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran

Using the method described in 5c, the product from 62c (260mg, 0.36mmol) was deprotected to give the title compound (158mg, 87%); ν_{max} (KBr) 3424, 1715, 1603, 1507, 1452cm⁻¹; λ_{max} (EtOH) 324.5nm (ε_M 22,418); δ_H (CDCl₃) *inter alia* 0.92 (3H, d, 7.1Hz, 17-H₃), 1.22 (3H, d, *J* 6.3Hz, 14-H₃), 5.09 (2H, s, 1"-H), 6.20 (1H, s, 2-H), 6.40 (1H, dd, *J* 1.9, 3.1Hz, 4""-H), 6.47 (1H, d, *J* 3.1Hz, 3""-H), 7.04 (2H, d, *J* 8.9Hz, 3',5'-H₂), 7.88 (2H, d, *J* 8.9Hz, 2',6'-H₂); δ_C (CDCl₃) 12.7 (C-17), 20.8 (C-14), 31.6

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- (C-9), 39.6 (C-8), 42.5 (C-4), 42.8 (C-12), 54.2 (C-10), 61.3 (C-11), 62.4 (C-16), 65.6 (C-1"), 69.1 (C-7), 70.3 (C-6), 71.3 (C-13), 73.9 (C-5), 96.6 (C-2), 110.4 (C-3""), 110.6 (C-4""), 127.3 (C-1'), 129.2 (C-2',6'), 143.6 (C-5""), 149.5 (C-2"""), 162.0 (C-4'), 182.7 (C-1), 194.2 (C-3); m/z (NH₃ DCI) 503 (MH⁺, 5 85%), 83 (100%). The ¹H n.m.r. spectrum indicated that the title compound was essentially in the enolic form.

Biological Data

- 10 The activity of the Examples 1 to 62 against various bacteria* which are important in the diseases of humans was assayed in vitro using serial dilutions in nutrient agar with 5% chcolated horse blood.
- 15 The MIC's were determined after incubation for 18h at 37°C and values in the range 0.03 to 128 mg/ml⁻¹ were observed.

- * H. influenzae Q1;
B. catarrhalis 1502;
20 S. pyogenes CN10;
S. pneumoniae PU7; and
S. aureus Oxford.
- 25 The antibacterial activity of compounds of the instant invention against Legionella organisms are assayed in the following manner:

- All compounds to be tested are dissolved in distilled water.
- 30 Organism: L.pneumophila 1624, serogroup 1. The culture is thawed from frozen skim milk stocks and streaked onto supplemented buffered charcoal yeast extract agar (BCYE α , Oxoid). Three days later, colonies are suspended into tissue culture medium (TCM=Eagle's Minimal Essential Medium + Earles' salts supplemented with 10% foetal calf serum, 2mM L-glutamine and 1% non-essential amino acids) to 35 MacFarland's barium sulphate opacity standard 0.5. The suspension is further diluted 1:100 in TCM to yield a final inoculum of 4.83 x 10⁶

cfu/ml.

Inoculation of cells: Human foetal lung fibroblast (MRC-5) cells are grown to 80% confluence in 6-well plates. The medium is removed and 5 the monolayers washed twice with Dulbecco's PBS and the inoculum added.

Dosing: Sixteen hours after infection (time 0h), the medium is removed and the inoculated monolayers washed twice to remove any adherent, 10 non-intracellular, organisms. The compounds are prepared to the required concentrations (0.5, 2 and 8 μ g/ml) in TCM, and added to the cells. Erythromycin at 0.5 and 2 μ g/m is used as a control.

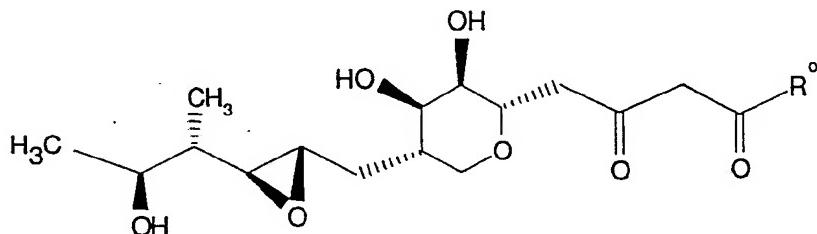
Sampling: At 0, 3, 12, 24, 36, 48 and 72h after the dose, the medium is 15 removed from one well/treatment, and the monolayers washed twice. Sterile distilled water is added and left for 30 min to lyse the cells. After vigorous trituration, the lysate is serially diluted in Mueller Hinton brother and plated onto BYCE α and 5% horse blood agars. Colonies of L.pneumophila are counted after 72h incubation at 37°C.

Stability tests: The stability of the compounds in TCM is also examined 20 over a 72h period. Solutions of 2 μ g/ml of each of the compounds to prepared in TCM and incubated at 37°C or 4°C and aliquots are removed at intervals. The compounds of formula (I) are assayed against Bacillus 25 subtilis ATCC 6633 and erythromycin lactobionate against Sarcina lutea NCTC 8340, using standards prepared in TCM.

Claim Set A:

What is claimed is:

- 5 1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:



wherein

10 R^o is $(A)_n - (B)_m$;

n and m are integers having a value of 0 or 1; provided that m and n may not both represent 0; and that when n is 0 then A represents a bond; and when m is 0 then B represents hydrogen;

A is an optionally substituted (C_{1-6}) alkyl, (C_{2-6}) alkenyl, or (C_{2-6}) alkynyl group;

15 and

B is an optionally substituted (C_{3-7}) cycloalkyl, (C_{4-7}) cycloalkenyl, aryl, heterocyclyl or heteroaryl group.

20 2. A compound according to Claim 1 wherein n is 0 and m is 1, and B is a substituted or unsubstituted (C_{4-7}) cycloalkenyl, aryl, heterocyclyl or heteroaryl group.

25 3. A compound according to Claim 1 or 2 wherein B is an optionally substituted cyclohexenyl, phenyl, furanyl, thieryl, pyridinyl, pyrimidinyl, pyrazolyl, oxazolyl, or thiazolyl group.

30 4. A compound according to any one of Claims 1 to 3 wherein the optional substituents are independently selected up to five times by (C_{1-6})alkyl, (poly)halo(C_{1-6})alkyl, cyano, (un)substituted heterocyclyl, amino, (C_{1-6})alkanoylamino, (un)substituted mono- or di-(C_{1-6})alkylamino, hydroxy, (C_{1-6})alkoxy, -O-R₁, (C_{1-6})alkenoxy, hydroxy substituted (C_{1-6})alkoxy, (un)substituted heterocyclylthio, arylthio, arylsulphinyl, arylsulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl,

(C₁₋₆)alkylsulphonyl, (un)substituted sulphamoyl, (un)substituted carbamoyl, amidino, guanidino, nitro, halogen, carboxy and salts and esters thereof, (C₁₋₆) alkylcarbonyloxy, arylcarbonyloxy, heterocyclcarbonyloxy, or acyl groups.

5

5. A compound according to Claim 4 wherein R₁ is selected from (C₂₋₆) alkenyl, (C₁₋₆) alkoxy alkyl, (poly)hydroxy (C₁₋₆) alkyl, (poly)halo(C₁₋₆) alkyl, (un)substituted heteroaryl (C₁₋₆) alkyl, (un)substituted mono- or di- amino (C₁₋₆) alkyl, (un)substituted heterocycl (C₁₋₆) alkyl, or N-(C₁₋₆ alkyl)-N- heteroaryl-(C₁₋₆)alkyl.

- 10 6. A compound according to Claim 4 wherein the optional substituents are selected from methoxy, C(O)CH₃, methyl, cyano, chloro, fluoro, bromo, -CH(OCH₂CH₃)₂, nitro, -CH(O), N(CH₃)₂, SCH₃, S(O)CH₃, S(O)₂CH₃, -CH₂OH, piperidine, O-CF₃, hydroxy, ethenyloxy, 2-hydroxyethoxy, N-(2-hydroxyethyl)-N-methylamino, 3-hydroxypropyloxy, azidoethoxy, N-methyl-N-pyridylaminoethoxy, piperidinylethoxy, pyridylmethyloxy, nitrofuranyl methyloxy, or furanymethyloxy.

- 15 20 7. A compound according to Claim 1 or 3 wherein n is 1, m is 0 and B is hydrogen.

8. A compound according to Claim 1 or 3 wherein n and m are both 1.

- 25 9. A compound according to Claim 1 which is:

3R,4R-Dihydroxy-2S-[2,4-Dioxo-4-(4-methoxyphenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

- 30 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methoxypyrid-5-yl)-but-1-yl]-5S-(2S,3S,epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-nitrophenyl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)-tetrahydropyran;

- 35 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(2-methylthiopyrid-5-yl)-but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;

- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methylthiophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[4-(2-chloropyrid-5-yl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-fluorophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 10 3R,4R Dihydroxy-2S-[4-(4-allyloxyphenyl)-2,4-dioxobut-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 15 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-methoxymethyloxophenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran;
- 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-hydroxyethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran; or
- 20 3R,4R-Dihydroxy-2S-[2,4-dioxo-4-(4-{2-azidoethoxy}phenyl)but-1-yl]-5S-(2S,3S-epoxy-5S-hydroxy-4S-methylhexyl)tetrahydropyran.
10. A compound according to claim 1 substantially as hereinbefore defined with reference to any one of the Examples.
- 25 11. A pharmaceutical composition comprising a compound according to anyone of claims 1 to 9, and a pharmaceutically acceptable carrier thereof.
12. A compound according to any one of claims 1 to 9 for use as an active therapeutic substance.
- 30 13. A compound according to any one of claims 1 to 9 for use in treating bacterial and mycoplasmal infections.
14. Use of a compound according to any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of bacterial and mycoplasmal infections.
- 35

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 92/01760

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1. 5 C07H19/01;	C07D405/14;	C07D407/06;	C07D407/14
C07D409/14;	C07D413/14;	C07D417/14;	A61K31/70

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols		
Int.C1. 5	C07H	;	C07D ; A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	JOURNAL OF MEDICINAL CHEMISTRY. vol. 32, no. 1, January 1989, WASHINGTON US pages 151 - 160 KLEIN L.L. ET AL 'Synthesis and activity of nonhydrolyzable pseudomonic acid analog' cited in the application see page 153 ---	1, 12
A	EP,A;0 090 603 (BEECHAM GROUP PLC) 5 October 1983 see examples ---	19 -/-

¹⁰ Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

¹¹ "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention¹² "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step¹³ "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art¹⁴ "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

16 DECEMBER 1992

Date of Mailing of this International Search Report

13. 01. 93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

DAY G.J.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1 no. 1, January 1985, LETCHWORTH GB pages 549 - 555 CRIMMIN M.J. ET AL 'The chemistry of pseudomonic acid. Part 8. Electrophilic substitutions at C-2 and C-15 of the pseudomonic acid nucleus by means of lithium dienolates' cited in the application see page 549 - page 551 -----	19

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9201760
SA 64805**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 16/12/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0090603	05-10-83	JP-A- 58174379	13-10-83